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(57) Abstract

A method and solution for perioperatively inhibiting a variety of pain and inflammation and spasm processes at a wound. The solution includes multiple pain and inflammation inhibitory agents and spasm inhibitory agents at dilute concentration in a physiologic base, such as saline or lactated Ringer's solution. Depending on the application, the pain and inflammation agents included in the solution may include: (1) serotonin receptor antagonists; (2) serotonin receptor agonists; (3) histamine receptor antagonists; (4) bradykinin receptor antagonists; (5) kallikrein inhibitors; (6) tachykinin receptor antagonists, including neurokinin$_1$ and neurokinin$_2$ receptor subtype antagonists; (7) calcitonin gene-related peptide (CGRP) receptor antagonists; (8) interleukin receptor antagonists; (9) inhibitors of enzymes active in the synthetic pathway for arachadonic acid metabolites, including (a) phospholipase inhibitors, including PLA_2 isoform and PLC_γ isoform inhibitors, (b) cyclooxygenase inhibitors, and (c) lipooxygenase inhibitors; (10) prostanoid receptor antagonists including eicosanoid EP-1 and EP-2 receptor subtype antagonists and thromboxane receptor subtype antagonists; (11) leukotriene receptor antagonists including leukotriene B_4 and D_4 receptor subtype antagonists; (12) opioid receptor agonists, including mu-opiate, delta-opiate, and kappa-opiate receptor sybtype agonists; (13) purinoceptor agonists and antagonists including P_{2X} receptor antagonists and P_{2Y} receptor agonists; (14) adenosine triphosphate (ATP)-sensitive potassium channel openers; and (15) calcium channel antagonists. Suitable anti-inflammatory/anti-pain agents which also act as anti-spasm agents include serotonin receptor antagonists, tachykinin receptor antagonists, ATP-sensitive potassium channel openers and calcium channel antagonists. Other agents which may be utilized in the solution specifically for their anti-spasm properties including endothelin receptor antagonists and the nitric oxyde donors (enzyme activators). The solution is used to continuously irrigate a wound during an operative/interventional procedure for preemptive inhibition of pain and inflammation, as well as vascular and smooth muscle spasm, while avoiding undesirable side effects associated with oral, intramuscular or intravenous application of larger doses of the agents. The solution is useful for arthroscopic, intravascular and urologic procedures, as well as for application to burns, and intra- and postoperative application to surgical wounds.

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A. CLASSIFICATION OF SUBJECT MATTER
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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US,A,5 272 139 (CARY JR) 21 December 1993 see the whole document ---	1
A	EP,A,0 364 266 (RETINA FOUNDATION INC.) 18 April 1990 ---	
A	EP,A,0 539 886 (LUITPOLD PHARMA GMBH) 5 May 1993 ---	
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Date of the actual completion of the international search	Date of mailing of the international search report
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European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Klaver, T

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		DE-D-	3751059	23-03-95
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IRRIGATION SOLUTION AND METHOD FOR INHIBITION OF PAIN, INFLAMMATION AND SPASM

I. Field of the Invention

The present invention relates to surgical irrigation solutions and methods, and particularly for anti-inflammatory, and anti-pain and anti-spasm surgical irrigation solutions.

II. Background of the Invention

Arthroscopy is a surgical procedure in which a camera, attached to a remote light source and video monitor, is inserted into an anatomic joint (e.g., knee, shoulder, etc.) through a small portal incision in the overlying skin and joint capsule. Through similar portal incisions, surgical instruments may be placed in the joint, their use guided by arthroscopic visualization. As arthroscopists' skills have improved, an increasing number of operative procedures, once performed by "open" surgical technique, now can be accomplished arthroscopically. Such procedures include, for example, partial meniscectiomies and ligament reconstructions in the knee, shoulder acromioplasties and rotator cuff debridements and elbow synovectomies. As a result of widening surgical indications and the development of small diameter arthroscopes, wrist and ankle arthroscopies also have become routine.

Throughout each arthroscopy, physiologic irrigation fluid (e.g., normal saline or lactated Ringer's) is flushed continuously through the joint, distending the joint capsule and removing operative debris, thereby providing clearer intra-articular visualization. U.S. Patent 4,504,493 to Marshall discloses an isomolar solution of

glycerol in water for a non-conductive and optically clear irrigation solution for arthroscopy.

Irrigation is also used in other procedures, such as intravascular diagnostic and therapeutic procedures, urologic procedures and the treatment of burns and any operative wounds. In each case, a physiologic fluid is used to irrigate a wound or body cavity or passage. Conventional physiologic irrigation fluids do not provide analgesic or anti-inflammatory effects.

Alleviating pain and suffering in postoperative patients is an area of special focus in clinical medicine, especially with the growing number of out-patient operations performed each year. The most widely used agents, cyclooxygenase inhibitors (e.g., ibuprofen) and opioids (e.g., morphine, fentanyl) have significant side effects, including gastrointestinal irritation/bleeding and respiratory depression. The high incidence of nausea and vomiting related to opioids is especially problematic in the postoperative period. Therapeutic agents aimed at treating postoperative pain while avoiding detrimental side effects are not easily developed because the molecular targets for these agents are distributed widely throughout the body and mediate diverse physiological actions. Despite the significant clinical need to inhibit pain and inflammation, as well as vasospasm and smooth muscle spasm, methods for the delivery of pain, inflammation and spasm inhibitors at effective dosages while minimizing adverse systemic side effects have not been developed. As an example, conventional (i.e., intravenous, oral or intramuscular) methods of administration of opiate agonists in therapeutic doses frequently is associated with significant adverse side effects, including severe respiratory depression, changes in mood and mental clouding and profound nausea and vomiting.

Prior studies have demonstrated the ability of endogenous agents, such as serotonin (5-hydroxytryptamine, sometimes referred to herein as "5-HT"), bradykinin and histamine, to produce pain and inflammation. Sicuteri, F., et. al., *Serotonin-Bradykinin Potentiation in the Pain Receptors in Man*, Life Sci. 4, pp. 309-316 (1965); Rosenthal, S.R., *Histamine as the Chemical Mediator for Cutaneous Pain*, J. Invest. Dermat. 69, pp. 98-105 (1977); Richardson, B.P., et. al., *Identification of Serotonin M-Receptor Subtypes and their Specific Blockade by a New Class of Drugs*, Nature 316, pp. 126-131 (1985); Whalley, E.T., et. al., *The Effect of Kinin Agonists and Antagonists*, Naunyn-Schmiedeb Arch. Pharmacol. 36, pp. 652-57 (1987); Lang, E., et. al., *Chemo-Sensitivity of Fine Afferents from Rat Skin In Vitro*, J. Neurophysiol. 63, pp. 887-901 (1990).

For example, 5-HT applied to a human blister base (denuded skin) has been demonstrated to cause pain that can be inhibited by 5-HT_3 receptor antagonists. Richardson et al., 1985. Similarly, peripherally-applied bradykinin produces pain which can be blocked by bradykinin receptor antagonists. Sicuteri et al., 1965; Whalley et al., 1987; Dray, A., et. al., *Bradykinin and Inflammatory Pain*, Trends Neurosci. 16, pp. 99-104 (1993). Peripherally-applied histamine produces vasodilation, itching and pain which can be inhibited by histamine receptor antagonists. Rosenthal, 1977; Douglas, W.W., "Histamine and 5-Hydroxytryptamine (Serotonin) and their Antagonists", in Goodman, L.S., et. al., ed., *The Pharmacological Basis of Therapeutics*, MacMillan Publishing Company, New York, pp. 605-638 (1985); Rumore, M.M., et. al., *Analgesic Effects of Antihistaminics*, Life Sci 36, pp. 403-416 (1985). Combinations of these three agonists (5-HT, bradykinin and histamine) applied together have been demonstrated to display a synergistic pain causing effect, producing a long-lasting and intense pain signal. Sicuteri et al., 1965; Richardson et al., 1985; Kessler, W., et. al., *Excitation of Cutaneous Afferent Nerve Endings In Vitro by a Combination of Inflammatory Mediators and Conditioning Effect of Substance P*, Exp. Brain Res. 91, pp. 467-476 (1992).

In the body, 5-HT is located in platelets and in central neurons, histamine is found in mast cells, and bradykinin is produced from a larger precursor molecule during tissue trauma, pH changes, temperature changes, etc. Because 5-HT can be released in large amounts from platelets at sites of tissue injury, producing plasma levels 20-fold greater than resting levels (Ashton, J.H., et. al., *Serotonin as a Mediator of Cyclic Flow Variations in Stenosed Canine Coronary Arteries*, Circulation 73, pp. 572-578 (1986)), it is possible that endogenous 5-HT plays a role in producing postoperative pain, hyperalgesia and inflammation. In fact, activated platelets have been shown to excite peripheral nociceptors *in vitro*. Ringkamp, M., et. al., *Activated Human Platelets in Plasma Excite Nociceptors in Rat Skin, In Vitro*, Neurosci. Lett. 170, pp. 103-106 (1994)). Similarly, histamine and bradykinin also are released into tissues during trauma. Kimura, E., et. al., *Changes in Bradykinin Level in Coronary Sinus Blood After the Experimental Occlusion of a Coronary Artery*, Am Heart J. 85, pp. 635-647 (1973); Douglas, 1985; Dray et. al. (1993).

In addition, prostaglandins also are known to cause pain and inflammation. Cyclooxygenase inhibitors, e.g., ibuprofen, are commonly used to block the production of prostaglandins, thereby reducing prostaglandin-mediated pain and inflammation. Flower, R.J., et. al., *Analgesic-Antipyretics and Anti-Inflammatory Agents; Drugs Employed in the Treatment of Gout*, in Goodman, L.S., et. al., ed.,

The Pharmacological Basis of Therapeutics, MacMillan Publishing Company, New York, pp. 674-715 (1985). Cyclooxygenase inhibitors are associated with some adverse systemic side effects when applied conventionally. For example, indomethacin or keterolac have well recognized gastrointestinal and renal adverse side effects.

As discussed, 5-HT, histamine, bradykinin and prostaglandins cause pain and inflammation. The various receptors through which these agents mediate their effects on peripheral tissues have been known and/or debated for the past two decades. Most studies have been performed in rats or other animal models. However, there are differences in pharmacology and receptor sequences between human and animal species. There have been no studies conclusively demonstrating the importance of 5-HT, bradykinin or histamine in producing postoperative pain in humans.

Furthermore, antagonists of these mediators currently are not used for postoperative pain treatment. A class of drugs, termed 5-HT and norepinephrine uptake antagonists, which includes amitriptyline, has been used orally with moderate success for chronic pain conditions. However, the mechanisms of chronic versus acute pain states are thought to be considerably different. In fact, two studies in the acute pain setting using amitriptyline perioperatively have shown no pain-relieving effect of amitriptyline. Levine, J.D., et. al., *Desipramine Enhances Opiate Postoperative Analgesia*, Pain 27, pp. 45-49 (1986); Kerrick, J.M., et. al., *Low-Dose Amitriptyline as an Adjunct to Opioids for Postoperative Orthopedic Pain: a Placebo-Controlled Trial Period*, Pain 52, pp. 325-30 (1993). In both studies the drug was given orally. The second study noted that oral amitriptyline actually produced a lower overall sense of well-being in postoperative patients, which may be due to the drug's affinity for multiple amine receptors in the brain.

Amitriptyline, in addition to blocking the uptake of 5-HT and norepinephrine, is a potent 5-HT receptor antagonist. Therefore, the lack of efficacy in reducing postoperative pain in the previously-mentioned studies would appear to conflict with the proposal of a role for endogenous 5-HT in acute pain. There are a number of reasons for the lack of acute pain relief found with amitriptyline in these two studies. (1) The first study used amitriptyline preoperatively for one week up until the night prior to surgery whereas the second study only used amitriptyline postoperatively. Therefore, no amitriptyline was present in the operative site tissues during the actual tissue injury phase, the time at which 5-HT is purported to be released. (2) Amitriptyline is known to be extensively metabolized by the liver. With oral administration, the concentration of amitriptyline in the operative site tissues may not

have been sufficiently high for a long enough time period to inhibit the activity of postoperatively released 5-HT in the second study. (3) Since multiple inflammatory mediators exist, and studies have demonstrated synergism between the inflammatory mediators, blocking only one agent (5-HT) may not sufficiently inhibit the inflammatory response to tissue injury.

There have been a few studies demonstrating the ability of extremely high concentrations (1% - 3% solutions -- i.e., 10 - 30 mg per milliliter) of histamine$_1$ (H_1) receptor antagonists to act as local anesthetics for surgical procedures. This anesthetic effect is not believed to be mediated via H_1 receptors but, rather, due to a non-specific interaction with neuronal membrane sodium channels (similar to the action of lidocaine). Given the side effects (e.g., sedation) associated with these high "anesthetic" concentrations of histamine receptor antagonists, local administration of histamine receptor antagonists currently is not used in the perioperative setting.

III. Summary of the Invention

The present invention provides a low-dose (i.e., dilute) solution constituting a mixture of multiple agents directed at inhibiting locally the mediators of pain and inflammation in a physiologic electrolyte carrier fluid. The invention also provides a method for perioperative delivery of the irrigation solution containing these agents directly to a surgical site, where it works locally at the neuroreceptor level to preemptively limit pain and inflammation at the site. The anti-pain/anti-inflammation agents in the solution include agents selected from the following classes of receptor antagonists, receptor agonists and enzyme inhibitors, each class acting through a differing molecular mechanism of action for pain and inflammation inhibition: (1) serotonin receptor antagonists; (2) serotonin receptor agonists; (3) histamine receptor antagonists; (4) bradykinin receptor antagonists; (5) kallikrein inhibitors; (6) tachykinin receptor antagonists, including neurokinin$_1$ and neurokinin$_2$ receptor subtype antagonists; (7) calcitonin gene-related peptide (CGRP) receptor antagonists; (8) interleukin receptor antagonists; (9) inhibitors of enzymes active in the synthetic pathway for arachadonic acid metabolites, including (a) phospholipase inhibitors, including PLA_2 isoform inhibitors and PLC_γ isoform inhibitors, (b) cyclooxygenase inhibitors, and (c) lipooxygenase inhibitors; (10) prostanoid receptor antagonists including eicosanoid EP-1 and EP-4 receptor subtype antagonists and thromboxane receptor subtype antagonists; (11) leukotriene receptor antagonists including leukotriene B_4 receptor subtype antagonists and leukotriene D_4 receptor subtype

antagonists; (12) opioid receptor agonists, including mu-opiate, delta-opiate, and kappa-opiate receptor subtype agonists; (13) purinoceptor agonists and antagonists including P_{2X} receptor antagonists and P_{2Y} receptor agonists; (14) adenosine triphosphate (ATP)-sensitive potassium channel openers; and (15) calcium channel antagonists. Each of the above agents functions both as an anti-inflammatory agent and as an anti-nociceptive, i.e., anti-pain or analgesic, agent. The selection of agents from these classes of compounds is tailored for the particular application.

Several preferred embodiments of the solution of the present invention also include anti-spasm agents for particular applications. For example, anti-spasm agents may be included in solutions used for vascular procedures to limit vasospasm, and for urinary procedures to limit spasms in the urinary tract and bladder wall. For such applications, an anti-spasm agent is utilized in the solution. For example, an anti-pain/anti-inflammation agent which also serves as an anti-spasm agent may be included. Suitable anti-inflammatory/anti-pain agents which also act as anti-spasm agents include serotonin receptor antagonists, tachykinin receptor antagonists, ATP-sensitive potassium channel openers and calcium channel antagonists. Other agents which may be utilized in the solution specifically for their anti-spasm properties including endothelin receptor antagonists and the nitric oxide donors (enzyme activators).

The present invention also provides a method for manufacturing a medicament compounded as a dilute irrigation solution for use in continuously irrigating an operative site or wound during an operative procedure. The method entails dissolving in a physiologic electrolyte carrier fluid a plurality of anti-pain/anti-inflammatory agents, and for some applications anti-spasm agents, each agent included at a concentration of preferably no more than 100,000 nanomolar, and more preferably no more than 10,000 nanomolar.

The method of the present invention provides for the delivery of a dilute combination of multiple antagonists to the mediators of pain, inflammation and spasm and inhibitory receptor agonists directly to a wound, such as the joint tissue during arthroscopic procedures. Since the active ingredients in the solution are being applied directly to the operative tissues in a continuous fashion, the drugs may be used efficaciously at extremely low doses relative to those doses required for therapeutic effect when the same drugs are delivered orally, intramuscularly or intravascularly. The advantage of low doses of agents is three-fold. The most important is the absence of systemic side effects which often limit the usefulness of these agents. The low therapeutic dosages utilized in the solution of the present invention minimize

intravascular absorption of the included agents, thereby also minimizing systemic effects. Additionally, the agents selected for particular applications in the solutions of the present invention are highly specific with regard to the mediators on which they work. This specificity is maintained by the low dosages utilized. Finally, the cost of these active agents per liter is extremely low.

Local administration of the agents via irrigation also guarantees a known concentration at the peripheral target site, regardless of interpatient variability in metabolism, blood flow, etc. Because of the direct mode of delivery, a therapeutic concentration is obtained instantaneously. Thus improved dosage control is provided. Local administration of the active agents directly to a wound or operative site also substantially reduces degradation of the agents through extracellular processes, i.e., first and second pass metabolism, that would otherwise occur if the agents were given orally, intravenously or intramuscularly. This is particularly true for those active agents that are peptides, which are metabolized rapidly. For example, some agents in the following classes are peptitic: bradykinin receptor antagonists; tachykinin receptor antagonists; opioid receptor agonists; CGRP receptor antagonists; and interleukin receptor antagonists. Local, continuous delivery to the wound or operative site minimizes degradation while also providing for the continuous replacement of that portion of the agent that may be degraded, to ensure that a local therapeutic concentration, sufficient to maintain receptor occupancy, is maintained throughout the duration of the operative procedure.

Local administration of the solution throughout a surgical procedure in accordance with the present invention produces a "preemptive analgesic" effect. By occupying the target receptors or inactivating targeted enzymes prior to the initiation of significant operative trauma locally, the agents of the present solution modulate signal transmission to preemptively inhibit the targeted pathologic process. If inflammatory mediators and processes are inhibited before they can exert tissue damage, the benefit is more substantial than if given after the damage has been initiated.

Inhibiting more than one inflammatory mediator by application of the multiple agent solution of the present invention is believed to dramatically reduce the degree of inflammation and pain. The irrigation solutions of the present invention include combinations of drugs, each effective against multiple anatomic receptors or enzymes. The drug agents are thus simultaneously effective against a combination of pathologic processes, including pain and inflammation, vasospasm and smooth muscle spasm. The action of these mediators is considered to be synergistic, in that the multiple

receptor antagonists and inhibitory agonists of the present invention provide a disproportionately increased efficacy in combination relative to the efficacy of the individual agents. The synergistic action of several of the agents of the present invention are discussed, by way of example, below in the detailed descriptions of those agents.

In addition to arthroscopy, the solution of the present invention may also be applied locally to any human body cavity or passage, operative wound, traumatic wound (e.g., burns) or in any operative/interventional procedure in which irrigation can be performed. These procedures include, but are not limited to, urological procedures, interventional cardiovascular diagnostic and/or therapeutic procedures, and oral, dental and periodontal procedures. As used herein throughout, the term "wound", unless otherwise specified, is intended to include surgical wounds, operative/interventional sites, traumatic wounds and burns.

Used intra-operatively, the solution should result in a clinically significant decrease in operative site pain and inflammation relative to currently-used irrigation fluids, thereby decreasing the patient's postoperative analgesic (i.e., opiate) requirement and, where appropriate, allowing earlier patient mobilization of the operative site. No extra effort on the part of the surgeon and operating room personnel is required to use the present solution relative to conventional irrigation fluids.

IV. Brief Description of the Drawings

The present invention will now be described in greater detail, by way of example, with reference to the accompanying drawings in which:

FIGURES 1, 2A and 2B provide charts of the percent of vasoconstriction versus time in control arteries, in the proximal segment of subject arteries, and in the distal segment of subject arteries, respectively, for the animal study described in EXAMPLE VII herein demonstrating the effect on vasoconstriction of infusion with histamine and serotonin antagonists, used in the solutions of the present invention, during balloon angioplasty; and

FIGURES 3 and 4 provide charts of plasma extravasation versus dosage of amitriptyline, used in the solutions of the present invention, delivered intravenously and intra-articularly, respectively, to knee joints in which extravasation has been induced by introduction of 5-Hydroxytryptamine in the animal study described in EXAMPLE VIII herein.

V. Detailed Description of the Preferred Embodiment

The irrigation solution of the present invention is a dilute solution of multiple pain/inflammation inhibitory agents and anti-spasm agents in a physiologic carrier. The carrier is a fluid containing physiologic electrolytes, such as normal saline or lactated Ringer's solution. The carrier is preferably a liquid, but for some applications, e.g., burns, may be compounded as a paste or salve.

The anti-inflammation/anti-pain agents are selected from the group consisting of: (1) serotonin receptor antagonists; (2) serotonin receptor agonists; (3) histamine receptor antagonists; (4) bradykinin receptor antagonists; (5) kallikrein inhibitors; (6) tachykinin receptor antagonists, including neurokinin$_1$ and neurokinin$_2$ receptor subtype antagonists; (7) calcitonin gene-related peptide (CGRP) receptor antagonists; (8) interleukin receptor antagonists; (9) inhibitors of enzymes active in the synthetic pathway for arachadonic acid metabolites, including (a) phospholipase inhibitors, including PLA_2 isoform inhibitors and PLC_γ isoform inhibitors (b) cyclooxygenase inhibitors, and (c) lipooxygenase inhibitors; (10) prostanoid receptor antagonists including eicosanoid EP-1 and EP-4 receptor subtype antagonists and thromboxane receptor subtype antagonists; (11) leukotriene receptor antagonists including leukotriene B_4 receptor subtype antagonists and leukotriene D_4 receptor subtype antagonists; (12) opioid receptor agonists, including mu-opiate, delta-opiate, and kappa-opiate receptor subtype agonists; (13) purinoceptor agonists and antagonists including P_{2X} receptor antagonists and P_{2Y} receptor agonists; (14) adenosine triphosphate (ATP)-sensitive potassium channel openers; and (15) calcium channel antagonists. Suitable anti-inflammatory/anti-pain agents which also act as anti-spasm agents include serotonin receptor antagonists, tachykinin receptor antagonists, ATP-sensitive potassium channel openers and calcium channel antagonists. Other agents which may be utilized in the solution specifically for their anti-spasm properties including endothelin receptor antagonists and the nitric oxide donors (enzyme activators).

In each of the surgical solutions of the present invention, the agents are included in low concentrations and are delivered locally in low doses relative to concentrations and doses required with conventional methods of drug administration to achieve the desired therapeutic effect. It is impossible to obtain an equivalent therapeutic effect by delivering similarly dosed agents via other (i.e., intravenous, intramuscular or oral) routes of drug administration since drugs given systemically are subject to first- and second-pass metabolism. Each agent is preferably included at a

low concentration of 0.1 to 10,000 nanomolar, except for cyclooxygenase inhibitors, which may be required at larger concentrations depending on the particular inhibitor selected. The exact agents selected for use in the solution, and the concentration of the agents, varies in accordance with the particular application, as described below.

A solution in accordance with the present invention can include just a single or multiple pain/inflammation inhibitory agent(s), a single or multiple anti-spasm agent(s), or a combination of both anti-spasm and pain/inflammation inhibitory agents from the enumerated classes, at low concentration. However, due to the aforementioned synergistic effect of multiple agents, and the desire to broadly block pain and inflammation, it is preferred that multiple agents be utilized.

The surgical solutions constitute a novel therapeutic approach to the delivery of multiple pharmacologic agents acting at distinct receptor and enzyme molecular targets. To date, pharmacologic strategies have focused on the development of highly specific drugs that are selective for individual receptor subtypes and enzyme isoforms that mediate responses to individual signaling neurotransmitters and hormones. As an example, endothelin peptides are some of the most potent vasoconstrictors known. Selective antagonists that are specific for subtypes of endothelin (ET) receptors are being sought by several pharmaceutical companies for use in the treatment of numerous disorders involving elevated endothelin levels in the body. Recognizing the potential role of the receptor subtype ET_A in hypertension, these drug companies specifically are targeting the development of selective antagonists to the ET_A receptor subtype for the anticipated treatment of coronary vasospasm. This standard pharmacologic strategy, although well accepted, is not optimal since many other vasoconstrictor agents (e.g., serotonin, prostaglandin, eicosanoid, etc.) simultaneously may be responsible for initiating and maintaining the vasospastic episode. Furthermore, despite inactivation of a single receptor subtype or enzyme, activation of other receptor subtypes or enzymes and the resultant signal transmission often can trigger a cascade effect. This explains the significant difficulty in employing a single receptor-specific drug to block a pathophysiologic process in which multiple transmitters play a role. Therefore, targeting only a specific individual receptor subtype, such as ET_A, is likely to be ineffective.

In contrast to the standard approach to pharmacologic therapy, the therapeutic approach of the present surgical solutions is based on the rationale that a combination of drugs acting simultaneously on distinct molecular targets is required to inhibit the full spectrum of events that underlie the development of a pathophysiologic state. Furthermore, instead of targeting a specific receptor subtype alone, the surgical

solutions are composed of drugs that target common molecular mechanisms operating in different cellular physiologic processes involved in the development of pain, inflammation, vasospasm, and smooth muscle spasm. In this way, the cascading of additional receptors and enzymes in the nociceptive, inflammatory and spasmodic pathways is minimized by the surgical solutions. In these pathophysiologic pathways, the surgical solutions inhibit the cascade effect both "upstream" and "downstream".

An example of "upstream" inhibition is the cyclooxygenase antagonists in the setting of pain and inflammation. The cyclooxygenase enzymes (COX_1 and COX_2) catalyze the conversion of arachidonic acid to prostaglandin H which is an intermediate in the biosynthesis of inflammatory and nociceptive mediators including prostaglandins, leukotrienes, and thromboxanes. The cyclooxygenase inhibitors block "upstream" the formation of these inflammatory and nociceptive mediators. This strategy precludes the need to block the interactions of the seven described subtypes of prostanoid receptors with their natural ligands. A similar "upstream" inhibitor included in the surgical solutions is aprotinin, a kallikrein inhibitor. The enzyme kallikrein, a serine protease, cleaves the high molecular weight kininogens in plasma to produce bradykinins, important mediators of pain and inflammation. By inhibition of kallikrein, aprotinin effectively inhibits the synthesis of bradykinins, thereby providing an effective "upstream" inhibition of these inflammatory mediators.

The surgical solutions also make use of "downstream" inhibitors to control the pathophysiologic pathways. In vascular smooth muscle preparations that have been precontracted with a variety of neurotransmitters (e.g., serotonin, histamine, endothelin, and thromboxane) implicated in coronary vasospasm, ATP-sensitive potassium channel openers (KCOs) produce smooth muscle relaxation which is concentration dependent (Quast et al., 1994; Kashiwabara et al., 1994). The KCOs, therefore, provide a significant advantage to the surgical solutions in the settings of vasospasm and smooth muscle spasm by providing "downstream" antispasmodic effects that are independent of the physiologic combination of agonists initiating the spasmodic event. Similarly, NO donors and voltage-gated calcium channel antagonists can limit vasospasm and smooth muscle spasm initiated by multiple mediators known to act earlier in the spasmodic pathway. These same calcium channel antagonists also can provide a "downstream" blockade of inflammation. Moncada, S., Flower, R. and Vane, J. in *Goodman's and Gilman's Pharmacological Basis of Therapeutics*, (7th ed.), MacMillan Publ. Inc., pp. 660-5 (1995).

The following is a description of suitable drugs falling in the aforementioned classes of anti-inflammation/anti-pain agents, as well as suitable concentrations for use

in solutions, of the present invention. While not wishing to be limited by theory, the justification behind the selection of the various classes of agents which is believed to render the agents operative is also set forth.

A. Serotonin Receptor Antagonists

Serotonin is thought to produce pain by stimulating serotonin$_2$ (5-HT$_2$) and/or serotonin$_3$ (5-HT$_3$) receptors on nociceptive neurons in the periphery. Most researchers agree that 5-HT$_3$ receptors on peripheral nociceptors mediate the immediate pain sensation produced by 5-HT (Richardson et al., 1985). In addition to inhibiting 5-HT-induced pain, 5-HT$_3$ receptor antagonists, by inhibiting nociceptor activation, also may inhibit neurogenic inflammation. Barnes P.J., et. al., *Modulation of Neurogenic Inflammation: Novel Approaches to Inflammatory Disease*, Trends in Pharmacological Sciences 11, pp. 185-189 (1990). A study in rat ankle joints, however, claims the 5-HT$_2$ receptor is responsible for nociceptor activation by 5-HT. Grubb, B.D., et. al., *A Study of 5-HT-Receptors Associated with Afferent Nerves Located in Normal and Inflamed Rat Ankle Joints*, Agents Actions 25, pp. 216-18 (1988). Therefore, activation of 5-HT$_2$ receptors also may play a role in peripheral pain and neurogenic inflammation.

One goal of the solution of the present invention is to block pain and a multitude of inflammatory processes. Thus 5-HT$_2$ and 5-HT$_3$ receptor antagonists are both suitably used, either individually or together, in the solution of the present invention, as shall be described subsequently. Amitriptyline (Elavil™) is a suitable 5-HT$_2$ receptor antagonist for use in the present invention. Amitriptyline has been used clinically for numerous years as an anti-depressant, and is found to have beneficial effects in certain chronic pain patients. Metoclopramide (Reglan™) is used clinically as an anti-emetic drug, but displays moderate affinity for the 5-HT$_3$ receptor and can inhibit the actions of 5-HT at this receptor, possibly inhibiting the pain due to 5-HT release from platelets. Thus it also is suitable for use in the present invention.

Other suitable 5-HT$_2$ receptor antagonists include imipramine, trazadone, desipramine and ketanserin. Ketanserin has been used clinically for its anti-hypertensive effects. Hedner, T., et. al., *Effects of a New Serotonin Antagonist, Ketanserin, in Experimental and Clinical Hypertension*, Am J of Hypertension, pp. 317s-23s (Jul. 1988). Other suitable 5-HT$_3$ receptor antagonists include cisapride and ondansetron. Suitable serotonin$_{1B}$ receptor antagonists include yohimbine, N-[-methoxy-3- (4-methyl-1-piperanzinyl)phenyl]-2'-methyl-4'- (5-methyl-1, 2, 4-oxadiazol-3-yl)[1, 1-biphenyl]-4-carboxamide ("GR127935") and methiothepin.

Therapeutic and preferred concentrations for use of these drugs in the solution of the present invention are set forth in Table 1.

Table 1
Therapeutic and Preferred Concentrations of
Pain/Inflammation Inhibitory Agents

Agent	Therapeutic Concentrations (Nanomolar)	Preferred Concentrations (Nanomolar)
Serotonin$_2$ Receptor Antagonists:		
amitriptyline	0.1 - 1,000	50 - 500
imipramine	0.1 - 1,000	50 - 500
trazodone	0.1 - 1,000	50 - 500
desipramine	0.1 - 1,000	50 - 500
ketanserin	0.1 - 1,000	50 - 500
Serotonin$_3$ Receptor Antagonists:		
metoclopramide	10 - 10,000	200 - 2,000
cisapride	0.1 - 1,000	20 - 200
ondansetron	0.1 - 1,000	20 - 200
Serotonin$_{1B}$ (Human 1D$_\beta$)Antagonists:		
yohimbine	0.1 - 1,000	50 - 500
GR127935	0.1 - 1,000	10 - 500
methiothepin	0.1 - 500	1 - 100

B. Serotonin Receptor Agonists

5-HT$_{1A}$, 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors are known to inhibit adenylate cyclase activity. Thus including a low dose of these serotonin$_{1A}$, serotonin$_{1B}$ and

serotonin$_{1D}$ receptor agonists in the solution should inhibit neurons mediating pain and inflammation. The same action is expected from serotonin$_{1E}$ and serotonin$_{1F}$ receptor agonists because these receptors also inhibit adenylate cyclase.

Buspirone is a suitable 1A receptor agonist for use in the present invention. Sumatriptan is a suitable 1A, 1B, 1D and 1F receptor agonist. A suitable 1B and 1D receptor agonist is dihydroergotamine. A suitable 1E receptor agonist is ergonovine. Therapeutic and preferred concentrations for these receptor agonists are provided in Table 2.

Table 2

Therapeutic and Preferred Concentrations of Pain/Inflammation Inhibitory Agents

Agent	Therapeutic Concentrations (Nanomolar)	Preferred Concentrations (Nanomolar)
Serotonin$_{1A}$ Agonists:		
buspirone	1 - 1,000	10 - 200
sumatriptan	1 - 1,000	10 - 200
Serotonin$_{1B}$ agonists:		
dihydroergotamine	0.1 - 1,000	10 - 100
sumatriptan	1 - 1,000	10 - 200
Serotonin$_{1D}$ Agonists:		
dihydroergotamine	0.1 - 1,000	10 - 100
sumatriptan	1 - 1,000	10 - 200
Serotonin$_{1E}$ Agonists:		
ergonovine	10 - 2,000	100 - 1,000
Serotonin$_{1F}$ Agonists:		
sumatriptan	1 - 1,000	10 - 200

C. Histamine Receptor Antagonists

Histamine receptors generally are divided into histamine$_1$ (H_1) and histamine$_2$ (H_2) subtypes. The classic inflammatory response to the peripheral administration of histamine is mediated via the H_1 receptor. Douglas, 1985. Therefore, the solution of the present invention preferably includes a histamine H_1 receptor antagonist. Promethazine (Phenergan™) is a commonly used anti-emetic drug which potently blocks H_1 receptors, and is suitable for use in the present invention. Interestingly, this drug also has been shown to possess local anesthetic effects but the concentrations necessary for this effect are several orders higher than that necessary to block H_1 receptors, thus, the effects are believed to occur by different mechanisms. The histamine receptor antagonist concentration in the solution is sufficient to inhibit H_1 receptors involved in nociceptor activation, but not to achieve a "local anesthetic" effect, thereby eliminating the concern regarding systemic side effects.

Histamine receptors also are known to mediate vasomotor tone in the coronary arteries. *In vitro* studies in the human heart have demonstrated that the histamine$_1$ receptor subtype mediates contraction of coronary smooth muscle. Ginsburg, R., et al., *Histamine Provocation of Clinical Coronary Artery Spasm: Implications Concerning Pathogenesis of Variant Angina Pectoris*, American Heart J., Vol. 102, pp. 819-822, (1980). Some studies suggest that histamine-induced hypercontractility in the human coronary system is most pronounced in the proximal arteries in the setting of atherosclerosis and the associated denudation of the arterial endothelium. Keitoku, M. et al., *Different Histamine Actions in Proximal and Distal Human Coronary Arteries in Vitro*, Cardiovascular Research 24, pp. 614-622, (1990). Therefore, histamine receptor antagonists may be included in the cardiovascular irrigation solution.

Other suitable H_1 receptor antagonists include terfenadine, diphenhydramine and amitriptyline. Because amitriptyline is also effective as a serotonin$_2$ receptor antagonist, it has a dual function as used in the present invention. Suitable therapeutic and preferred concentrations for each of these H_1 receptor antagonists are set forth in Table 3.

Table 3

Therapeutic and Preferred Concentrations of Pain/Inflammation Inhibitory Agents

Agent	Therapeutic Concentrations (Nanomolar)	Preferred Concentrations (Nanomolar)

Histamine$_1$ Receptor Antagonists:

promethazine	0.1 - 1,000	50 - 200
diphenhydramine	0.1 - 1,000	50 - 200
amitriptyline	0.1 - 1,000	50 - 500
terfenadine	0.1 - 1,000	50 - 500

D. Bradykinin Receptor Antagonists

Bradykinin receptors generally are divided into bradykinin$_1$ (B_1) and bradykinin$_2$ (B_2) subtypes. Studies have shown that acute peripheral pain and inflammation produced by bradykinin are mediated by the B_2 subtype whereas bradykinin-induced pain in the setting of chronic inflammation is mediated via the B_1 subtype. Perkins, M.N., et. al., *Antinociceptive Activity of the Bradykinin B1 and B2 Receptor Antagonists, des-Arg^9, [Leu^8]-BK and HOE 140, in Two Models of Persistent Hyperalgia in the Rat*, Pain 53, pp. 191-97 (1993); Dray, A., et. al., *Bradykinin and Inflammatory Pain*, Trends Neurosci 16, pp. 99-104 (1993), each of which references is hereby expressly incorporated by reference.

At present, bradykinin receptor antagonists are not used clinically. These drugs are peptides (small proteins), and thus they cannot be taken orally, because they would be digested. Antagonists to B_2 receptors block bradykinin-induced acute pain and inflammation. Dray et. al., 1993. B_1 receptor antagonists inhibit pain in chronic inflammatory conditions. Perkins et al., 1993; Dray et. al., 1993. Therefore, depending on the application, the solution of the present invention preferably includes either or both bradykinin B_1 and B_2 receptor antagonists. For example, arthroscopy is performed for both acute and chronic conditions, and thus an irrigation solution for arthroscopy could include both B_1 and B_2 receptor antagonists.

Suitable bradykinin receptor antagonists for use in the present invention include the following bradykinin$_1$ receptor antagonists: the [des-Arg^{10}] derivative of D-Arg-(Hyp^3-Thi^5-D-Tic^7-Oic^8)-BK ("the [des-Arg^{10}] derivative of HOE 140", available from Hoechst Pharmaceuticals); and [Leu^8] des-Arg^9-BK. Suitable bradykinin$_2$ receptor antagonists include: [D-Phe^7]-BK; D-Arg-(Hyp^3-Thi^{5,8}-D-Phe^7)-BK ("NPC 349"); D-Arg-(Hyp^3--D-Phe^7)-BK ("NPC 567"); and D-Arg-(Hyp^3-Thi^5-D-Tic^7-Oic^8)-BK ("HOE 140"). These compounds are more fully described in the previously incorporated Perkins et. al. 1993 and Dray

et. al. 1993 references. Suitable therapeutic and preferred concentrations are provided in Table 4.

Table 4
Therapeutic and Preferred Concentrations of Pain/Inflammation Inhibitory Agents

Agent	Therapeutic Concentrations (Nanomolar)	Preferred Concentrations (Nanomolar)
Bradykinin$_1$ Receptor Antagonists:		
[Leu^8] des-Arg^9-BK	1 - 1,000	50 - 500
[des-Arg^{10}] derivative of HOE 140	1 - 1,000	50 - 500
Bradykinin$_2$ Receptor Antagonists:		
[D-Phe^7]-BK	100 - 10,000	200 - 5,000
NPC 349	1 - 1,000	50 - 500
NPC 567	1 - 1,000	50 - 500
HOE 140	1 - 1,000	50 - 500

E. Kallikrein Inhibitors

The peptide Bradykinin is an important mediator of pain and inflammation, as noted previously. Bradykinin is produced as a cleavage product by the action of kallikrein on high molecular weight kininogens in plasma. Therefore kallikrein inhibitors are believed to be therapeutic in inhibiting bradykinin production and resultant pain and inflammation. A suitable kallikrein inhibitor for use in the present invention is aprotinin. Suitable concentrations for use in the solutions of the present invention are set forth below in Table 5.

Table 5
Therapeutic and Preferred Concentrations of Pain/Inflammation Inhibitory Agents

Agent	Therapeutic Concentrations (Nanomolar)	Preferred Concentrations (Nanomolar)
Kallikrein Inhibitor:		

Aprotinen	0.1 - 1,000	50 - 500 most prefer: 200

F. Tachykinin Receptor Antagonists

Tachykinins (TKs) are a family of structurally related peptides that include substance P, neurokinin A (NKA) and neurokinin B (NKB). Neurons are the major source of TKs in the periphery. An important general effect of TKs is neuronal stimulation, but other effects include endothelium-dependent vasodilation, plasma protein extravasation, mast cell degranulation and recruitment and stimulation of inflammatory cells. Maggi, C.A., *Gen. Pharmacol.*, Vol. 22, pp. 1-24 (1991). Due to the above combination of physiological action mediated by activation of TK receptors, targeting of TK receptors for promotion of analgesia and treatment of neurogenic inflammation.

1. Neurokinin$_1$ Receptor Subtype Antagonists

Substance P activates the neurokinin receptor subtype referred to as NK-1. Substance P is an undecapeptide that is present in sensory nerve terminals. Substance P is known to have multiple actions which produce inflammation and pain in the periphery after C-fiber activation, including vasodilation, plasma extravasation and degranulation of mast cells. Levine, J.D., et. al., *Peptides and the Primary Afferent Nociceptor*, J. Neurosci. 13, p. 2273 (1993). A suitable Substance P antagonist is ([D-Pro^9[spiro-gamma-lactam]Leu^{10},Trp^{11}]physalaemin-(1-11)) ("GR 82334"). Other suitable antagonists for use in the present invention which act on the NK-1 receptor are: 1-imino-2-(2-methoxy-phenyl)-ethyl)-7,7-diphenyl-4-perhydroisoindolone(3aR,7aR) ("RP 67580"); and 2s,3s-cis-3-(2-methoxybenzylamino)-2-benzhydrylquinuclidine ("CP 96,345"). Suitable concentrations for these agents are set forth in Table 6.

Table 6

Therapeutic and Preferred Concentrations of Pain/Inflammation Inhibitory Agents

Agent	Therapeutic Concentrations (Nanomolar)	Preferred Concentrations (Nanomolar)
Neurokinin$_1$ Receptor Subtype Antagonists		
GR 82334	1 - 1,000	10 - 500
CP 96,345	1-10,000	100-1,000

RP 67580	0.1-1,000	100-1,000

2. Neurokinin$_2$ Receptor Subtype Antagonists

Neurokinin A is a peptide which is colocalized in sensory neurons with substance P and which also promotes inflammation and pain. Neurokinin A activates the specific neurokinin receptor referred to as NK2. Edmonds-Alt, S., et. al., *A Potent and Selective Non-Peptide Antagonist of the Neurokinin A (NK_2) Receptor*, Life Sci. 50:PL101 (1992). In the urinary tract, TKs are powerful spasmogens acting through only the NK-2 receptor in the human bladder, as well as the human urethra and ureter. Maggi, C.A., *Gen. Pharmacol.*, Vol. 22, pp. 1-24 (1991). Thus, the desired drugs for inclusion in a surgical solution for use in urological procedures would contain an antagonist to the NK-2 receptor to reduce spasm. Examples of suitable NK2 antagonists include: ((S)-N-methyl-N-[4-(4-acetylamino-4-phenylpiperidino)-2- (3,4-dichlorophenyl)butyl]benzamide ("(±)-SR 48968"); Met-Asp-Trp-Phe-Dap-Leu ("MEN 10,627"); and cyc(Gln-Trp-Phe-Gly-Leu-Met) ("L 659,877"). Suitable concentrations of these agents are provided in Table 7.

Table 7

Therapeutic and Preferred Concentrations of Pain/Inflammation Inhibitory Agents

Agent	Therapeutic Concentrations (Nanomolar)	Preferred Concentrations (Nanomolar)
Neurokinin$_2$ Receptor Subtype Antagonists:		
MEN 10,627	1-1,000	10-1,000
L 659,877	10-10,000	100-10,000
(±)-SR 48968	10-10,000	100-10,000

G. CGRP Receptor Antagonists

Calcitonin gene-related peptide (CGRP) is a peptide which is also colocalized in sensory neurons with substance P, and which acts as a vasodilator and potentiates the actions of substance P. Brain, S.D., et. al., *Inflammatory Oedema Induced by Synergism Between Calcitonin Gene-Related Peptide (CGRP) and Mediators of Increased Vascular Permeability*, Br. J. Pharmacol. 99, p. 202 (1985). An example of a suitable CGRP receptor antagonist is alpha-CGRP-(8-37), a truncated version of

CGRP. This polypeptide inhibits the activation of CGRP receptors. Suitable concentrations for this agent are provided in Table 8.

Table 8
Therapeutic and Preferred Concentrations of Pain/Inflammation Inhibitory Agents

Agent	Therapeutic Concentrations (Nanomolar)	Preferred Concentrations (Nanomolar)
CGRP Receptor Antagonist:		
alpha-CGRP-(8-37)	1-1,000	10-500

H. Interleukin Receptor Antagonist

Interleukins are a family of peptides, classified as cytokines, produced by leukocytes and other cells in response to inflammatory mediators. Interleukins (IL) may be potent hyperalgesic agents peripherally. Ferriera, S.H., et. al., *Interleukin-1beta as a Potent Hyperalgesic Agent Antagonized by a Tripeptide Analogue*, Nature 334, p. 698 (1988). An example of a suitable IL-1beta receptor antagonist is Lys-D-Pro-Thr, which is a truncated version of IL-1beta. This tripeptide inhibits the activation of IL-1beta receptors. Suitable concentrations for this agent are provided in Table 9.

Table 9
Therapeutic and Preferred Concentrations of Pain/Inflammation Inhibitory Agents

Agent	Therapeutic Concentrations (Nanomolar)	Preferred Concentrations (Nanomolar)
Interleukin Receptor Antagonist:		
Lys-D-Pro-Thr	1-1,000	10-500

I. Inhibitors of Enzymes Active in the Synthetic Pathway for Arachidonic Acid Metabolites

1. Phospholipase Inhibitors

The production of arachidonic acid by phospholipase A_2 (PLA_2) results in a cascade of reactions that produces numerous mediators of inflammation, know as eicosanoids. There are a number of stages throughout this pathway that can be

inhibited, thereby decreasing the production of these inflammatory mediators. Examples of inhibition at these various stages are given below.

Inhibition of the enzyme PLA_2 isoform inhibits the release of arachidonic acid from cell membranes, and therefore inhibits the production of prostaglandins and leukotrienes resulting in the anti-inflammatory and analgesic properties of these compounds. Glaser, K.B., *Regulation of Phospholipase A2 Enzymes: Selective Inhibitors and Their Pharmacological Potential*, Adv. Pharmacol. 32, p. 31 (1995). An example of a suitable PLA_2 isoform agonist is manoalide. Suitable concentrations for this agent are included in Table 10. Inhibition of PLC_γ isoform also will result in decreased production of prostanoids and leukotrienes, and, therefore, will result in decreased pain and inflammation. An example of a PLC_γ isoform inhibitor is 1-[6-((17β-3-methoxyestra-1,3,5(10)-trien-17-yl)amino)hexyl]-1H-pyrrole-2,5-dione

Table 10

Therapeutic and Preferred Concentrations of Pain/Inflammation Inhibitory Agents

Agent	Therapeutic Concentrations (Nanomolar)	Preferred Concentrations (Nanomolar)
PLA_2 Isoform Inhibitor:		
manoalide	100-100,000	500-10,000

2. Cyclooxygenase Inhibitors

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used as anti-inflammatory, anti-pyretic, anti-thrombotic and analgesic agents. Lewis, R.A., *Prostaglandins and Leukotrienes*, In: Textbook of Rheumatology, 3d ed. (Kelley W.N., et. al., eds.), p. 258 (1989). The molecular targets for these drugs are type I and type II cyclooxygenases (COX-1 and COX-2). These enzymes are also known as Prostaglandin H Synthase 1 (constitutive) and 2 (inducible) (PGHS), and catalyze the conversion of arachidonic acid to Prostaglandin H which is an intermediate in the biosynthesis of prostaglandins and thromboxanes. The COX-2 enzyme has been identified in endothelial cells, macrophages, and fibroblasts. This enzyme is induced by IL-1 and endotoxin, and its expression is upregulated at sites of inflammation. Constitutive activity of COX-1 and induced activity of COX-2 both lead to synthesis of prostaglandins which contribute to pain and inflammation.

NSAIDs currently on the market (diclofenac, naproxen and indomethacin, ibuprofen, etc.) are generally nonselective inhibitors of both isoforms of COX, but

may show greater selectively for COX-1 over COX-2, although this ratio varies for the different compounds. Uses of COX-1 and 2 inhibitors to block formation of prostaglandins represents a better therapeutic strategy than attempting to block interactions of the natural ligands with the seven described subtypes of prostanoid receptors. Reported antagonists of the eicosanoid receptors (EP1, EP2, EP3) are quite rare and only specific, high affinity antagonists of the Thromboxane A2 receptor have been reported. Wallace, J. and Cirino, G. *Trends in Pharm. Sci.*, Vol. 15 pp. 405-406 (1994).

The use of cyclooxygenase inhibitors is contraindicated in patients with ulcer disease, gastritis or renal impairment. In the United States, the only available injectable form of this class of drugs is ketorolac (Toradol™), available from Syntex Pharmaceuticals, which is conventionally used intramuscularly or intravenously in postoperative patients but, again, is contraindicated for the above-mentioned categories of patients. The use of ketorolac, or any other cyclooxygenase inhibitor(s), in the solution in substantially lower concentrations than currently used perioperatively may allow the use of this drug in otherwise contraindicated patients. The addition of a cyclooxygenase inhibitor to the solutions of the present invention adds a distinct mechanism for inhibiting the production of pain and inflammation during arthroscopy or other operative/interventional procedure.

Preferred cyclooxygenase inhibitors for use in the present invention are keterolac and indomethacin. Of these two agents, indomethacin is less preferred because of the relatively high dosages required. Therapeutic and preferred concentrations for use in the solution are provided in Table 11.

Table 11

Therapeutic and Preferred Concentrations of Pain/Inflammation Inhibitory Agents

Agent	Therapeutic Concentrations (Nanomolar)	Preferred Concentrations (Nanomolar)
Cyclooxygenase Inhibitors:		
ketorolac	100 - 10,000	800 - 5,000
indomethacin	1,000 - 500,000	10,000 - 200,000 (most prefer: 10,000-100,000)

3. Lipooxygenase Inhibitors

Inhibition of the enzyme lipooxygenase inhibits the production of leukotrienes, such as leukotriene B_4, which is known to be an important mediator of inflammation and pain. Lewis, R.A., *Prostaglandins and Leukotrienes*, In: Textbook of Rheumatology, 3d ed. (Kelley W.N., et. al., eds.), p. 258 (1989). An example of a 5-lipooxygenase antagonist is 2,3,5-trimethyl-6-(12-hydroxy-5,10-dodecadiynyl)-1,4-benzoquinone ("AA 861"), suitable concentrations for which are listed in Table 12.

Table 12

Therapeutic and Preferred Concentrations of Pain/Inflammation Inhibitory Agents

Agent	Therapeutic Concentrations (Nanomolar)	Preferred Concentrations (Nanomolar)
Lipooxygenase Inhibitor:		
AA 861	100-10,000	500-5,000

J. Prostanoid Receptor Antagonists

Specific prostanoids produced as metabolites of arachidonic acid mediate their inflammatory effects through activation of prostanoid receptors. Examples of classes of specific prostanoid antagonists are the eicosanoid EP-1 and EP-4 receptor subtype antagonists and the thromboxane receptor subtype antagonists. A suitable prostaglandin E_2 receptor antagonist is 8-chlorodibenz[b,f][1,4]oxazepine-10(11H)-carboxylic acid, 2-acetylhydrazide ("SC 19220"). A suitable thromboxane receptor subtype antagonist is [15-[1α, 2β(5Z), 3β, 4α]-7-[3-[2-(phenylamino)-carbonyl] hydrazino] methyl]-7-oxobicyclo-[2,2,1]-hept-2-yl]-5-heptanoic acid ("SQ 29548"). Suitable concentrations for these agents are set forth in Table 13.

Table 13

Therapeutic and Preferred Concentrations of Pain/Inflammation Inhibitory Agents

Agent	Therapeutic Concentrations (Nanomolar)	Preferred Concentrations (Nanomolar)
Eicosanoid EP-1 Antagonist:		
SC 19220	100-10,000	500-5,000

K. Leukotriene Receptor Antagonists

The leukotrienes (LTB_4, LTC_4, and LTD_4) are products of the 5-lipoxygenase pathway of arachidonic acid metabolism that are generated enzymatically and have important biological properties. Leukotrienes are implicated in a number of pathological conditions including inflammation. Specific antagonists are currently being sought by many pharmaceutical companies for potential therapeutic intervention in these pathologies. Halushka, P.V., et al., Annu. Rev. Pharmacol. Toxicol. 29: 213-239 (1989); Ford-Hutchinson, A. Crit. Rev. Immunol. 10: 1-12 (1990). The LTB_4 receptor is found in certain immune cells including eosinophils and neutrophils. LTB_4 binding to these receptors results in chemotaxis and lysosomal enzyme release thereby contributing to the process of inflammation. The signal transduction process associated with activation of the LTB_4 receptor involved G-protein-mediated stimulation of phosphotidy (P1) metabolism and elevation of intracellular calcium.

An example of a suitable leukotriene B_4 receptor antagonist is SC (+)-(S)-7-(3-(2-(cyclopropylmethyl)-3-methoxy-4-[(methylamino)-carbonyl]phenoxy)propoxy)-3,4-dihydro-8-propyl-2H-1-benzopyran-2-propanoic acid ("SC 53228"). Concentrations for this agent that are suitable for the practice of the present invention are provided in Table 14. Other suitable leukotriene B_4 receptor antagonists include [3-[-2(7-chloro-2-quinolinyl)ethenyl]phenyl] [[3-(dimethylamino-3-oxopropyl)thio] methyl]thio propanoic acid ("MK 0571") and the drugs LY 66,071 and ICI 20,3219. MK 0571 also acts as a LTD_4 receptor subtype antagonist.

Table 14
Therapeutic and Preferred Concentrations of Pain/Inflammation Inhibitory Agents

Agent	Therapeutic Concentrations (Nanomolar)	Preferred Concentrations (Nanomolar)
Leukotriene B_4 Antagonist:		
SC 53228	100-10,000	500-5,000

L. Opioid Receptor Agonists

Opiate receptors are anti-nociceptive and, therefore, agonists to these receptors are desirable. Opiate receptors include the mu, delta and kappa opiate receptor subtypes. The mu receptors are located on sensory neuron terminals in the periphery and activation of these receptors inhibits sensory neuron activity. Basbaum, A.I., et. al., *Opiate analgesia: How Central is a Peripheral Target?*, N. Engl. J.

Med., 325:1168 (1991). Delta and kappa receptors are located on sympathetic efferent terminals and inhibit the release of prostaglandins, thereby inhibiting pain and inflammation. Taiwo, Y.O., et. al., *Kappa- and Delta-Opoids Block Sympathetically Dependent Hyperalgesia*, J. Neurosci., Vol. 11, page 928 (1991). Examples of suitable mu-opiate receptor agonists are fentanyl and Try-D-Ala-Gly-[N-MePhe]-NH(CH_2)$_2$ ("DAMGO"). An example of a suitable delta-opiate receptor agonist is [D-Pen^2,D-Pen^5]enkephalin ("DPDPE"). An example of a suitable kappa-opiate receptor agonist is (trans)-3,4-dichloro-N-methyl-N-[2-(1-pyrrolidnyl)cyclohexyl]-benzene acetamide ("U50,488"). Suitable concentrations for each of these agents are set forth in Table 15.

Table 15
Therapeutic and Preferred Concentrations of Pain/Inflammation Inhibitory Agents

Agent	Therapeutic Concentrations (Nanomolar)	Preferred Concentrations (Nanomolar)
Mu-Opiate Agonist:		
DAMGO	0.1-100	0.5-20
fentanyl	0.1-100	0.5-20
Delta-Opiate Agonist:		
DPDPE	0.1-500	1.0-100
Kappa-Opiate Agonist:		
U50,488	0.1-500	1.0-100

M. Purinoceptor Antagonists and Agonists

Extracellular ATP acts as a signaling molecule through interactions with P_2 purinoceptors. One major class of purinoceptors are the P_{2x} purinoceptors which are ligand-gated ion channels possessing intrinsic ion channels permeable to Na^+, K^+, and Ca^+. P_{2x} receptors described in sensory neurons are important for primary afferent neurotransmission and nociception. ATP is known to depolarize sensory neurons and plays a role in nociceptor activation since ATP released from damaged cells stimulates P_{2X} receptors leading to depolarization of nociceptive nerve-fibre terminals. The

P_{2X3} receptor has a highly restricted distribution (Chen, C.C., et. al., Nature, Vol. 377, pp. 428-431 (1995)) since it is selectively expressed in sensory C-fibre nerves that run into the spinal cord and many of these C-fibres are known to carry the receptors for painful stimuli. Thus, the highly restricted localization of expression for the P_{2X2} receptor subunits make these subtypes excellent targets for analgesic action.

Suitable antagonists of P_{2X}/ATP purinoceptors for use in the present invention include, by way of example, suramin and pyridoxylphosphate-6-azophenyl-2,4-disulfonic acid ("PPADS"). Suitable concentrations for these agents are provided in Table 16.

Agonists of the P_{2Y} receptor, a G-protein coupled receptor, are known to effect smooth muscle relaxation through elevation of IP3 levels with a subsequent increase in intracellular calcium. An example of a P_{2Y} receptor agonist is 2-me-S-ATP.

Table 16

Therapeutic and Preferred Concentrations of Pain/Inflammation Inhibitory Agents

Agent	Therapeutic Concentrations (Nanomolar)	Preferred Concentrations (Nanomolar)
Purinoceptor Antagonists:		
suramin	100-100,000	10,000-100,000
PPADS	100-100,000	10,000-100,000

N. Adenosine Triphosphate (ATP)-Sensitive Potassium Channel Openers

ATP-sensitive potassium channels have been discovered in numerous tissues, including brain, and binding studies using radiolabeled ligands have confirmed their existence. Opening of these channels causes potassium (K^+) efflux and hyperpolarizes the cell membrane. This hyperpolarization induces a reduction in intracellular free calcium through inhibition of voltage-dependent calcium (Ca^{2+}) channels and receptor operated Ca^{2+} channels. These combined actions drives the cell into a relaxed state, i.e. one which is more resistant to activation. K^+ channel openers (KCOs) have been shown to prevent stimulus coupled secretion and are considered to act on prejunctional neuronal receptors and thus will inhibit effects due to nerve stimulation and release of inflammatory mediators. Quast, U., et. al., *Cellular Pharmacology of*

Potassium Channel Openers in Vascular Smooth Muscle Cardiovasc. Res., Vol. 28, pp. 805-810 (1994).

ATP-sensitive potassium channels have been discovered in vascular and nonvascular smooth muscle and binding studies with radiolabeled ligands have confirmed their existence. Opening of these channels hyperpolarizes the cell membrane and in so doing, drives the smooth muscle cell into a relaxed state or one which is more resistant to activation, hence achieving vasorelaxation. K^+ channel openers (KCO) have been characterized as having potent antihypertensive activity *in vivo* and vasorelaxant activity *in vitro*. There is no known precedent in the medical literature demonstrating therapeutic utilization of these agents as anti-inflammatory, anti-nociceptive and bladder anti-spasm agents.

Synergistic interactions between endothelin (ET_A) antagonists and openers of ATP-sensitive potassium channels (KCOs) are expected in achieving vasorelaxation or smooth muscle relaxation. A rationale for dual use is based upon the fact that these drugs have different molecular mechanisms of action in promoting relaxation of smooth muscle and prevention of vasospasm. An initial intracellular calcium elevation in smooth muscle cells induced by ET_A receptor subsequently triggers activation of voltage-dependent channels and the entry of extracellular calcium which is required for contraction. Antagonists of the ET_A receptor will specifically block this receptor mediated effect but not block increases in calcium triggered by activation of other G-protein coupled receptors on the muscle cell.

Potassium-channel opener drugs, such as pinacidil, will open these channels causing K efflux and hyperpolarization of the cell membrane. This hyperpolarization will act to reduce contraction mediated by other receptors by the following mechanisms: (1) induces a reduction in intracellular free calcium through inhibition of voltage-dependent Ca channels by reducing the opening probability of both L-type and T-type calcium channels, (2) restrains agonist induced (receptor operated channels) Ca release from intracellular sources through inhibition of IP3 formation, and (3) lowers the efficiency of calcium as an activator of contractile proteins. Consequently, combined actions of these two classes of drugs will clamp the target cells into a relaxed state or one which is more resistant to activation.

Suitable ATP-Sensitive K^+ Channel Openers for the practice of the present invention include: (-)pinacidil; cromakalin; nicorandil; minoxidil; N-cyano-N'-[1,1-dimethyl-[2,2,3,3-^{3}H]propyl]-N"-(3-pyridinyl)guanidine ("P 1075"); and N-cyano-N'-(2-nitroxyethyl)-3-pyridinecarboximidamide monomethansulphonate ("KRN 2391"). Concentrations for these agents are set forth in Table 17.

Table 17
Therapeutic and Preferred Concentrations of Pain/Inflammation Inhibitory Agents

Agent	Therapeutic Concentrations (Nanomolar)	Preferred Concentrations (Nanomolar)
ATP-Sensitive K^+ Channel Opener:		
cromakalin	10-10,000	100-10,000
nicorandil	10-10,000	100-10,000
minoxidil	10-10,000	100-10,000
P 1075	0.1-1,000	10-1,000
KRN 2391	1-10,000	100-1,000
(-)pinacidil	1-10,000	100-1,000

O. Calcium Channel Antagonists

Calcium channel antagonists are a distinct group of drugs that interfere with the transmembrane flux of calcium ions required for activation of cellular responses mediating neuroinflammation. Calcium entry into platelets and white blood cells is a key event mediating activation of responses in these cells. Furthermore, the role of bradykinin receptors and neurokinin receptors (NK1 and NK2) in mediating neuroinflammation, signal transduction pathway includes increases in intracellular calcium, thus leading to activation of calcium channels on the plasma membrane. In many tissues, calcium channel antagonists, such as nifedipine, can reduce the release of arachidonic acid, prostaglandins, and leukotrienes that are evoked by various stimuli. Moncada, S., Flower, R. and Vane, J. in *Goodman's and Gilman's Pharmacological Basis of Therapeutics*, (7th ed.), MacMillan Publ. Inc., pp. 660-5 (1995).

Calcium channel antagonists also interfere with the transmembrane flux of calcium ions required by vascular smooth muscle for contractions. This effect provides the rationale for the use of calcium antagonists in the proposed use in perioperative procedures in which the goal is to alleviate vasospasm and relaxation of smooth muscle. The dihydropyridines, including nisoldipine act as specific inhibitors

(antagonists) of the voltage-dependent gating of the L-type subtype of calcium channels. Systemic administration of the calcium channel antagonist nifedipine during cardiac surgery has been previously utilized to prevent or minimize coronary artery vasospasm. Seitelberger, R., et. al., Circulation, Vol. 83, pp. 460-468 (1991). Again, there is no known precedent in the medical literature demonstrating therapeutic utilization of these agents as anti-inflammatory, anti-nociceptive and bladder anti-spasm agents.

Calcium channel antagonists, which are among the anti-pain/inflammation/spasm agents useful in the present invention, exhibit synergistic effect when combined with other agents of the present invention. Calcium (Ca^{2+}) channel antagonists and nitric oxide (NO) donors interact in achieving vasorelaxation or smooth muscle relaxation, i.e., in inhibiting spasm activity. A rationale for dual use is based upon the fact that these drugs have different molecular mechanisms of action, may not be completely effective in achieving relaxation used alone, and may have different time periods of effectiveness. In fact, there are numerous studies showing that calcium channel antagonists alone cannot achieve complete relaxation of vascular muscle that has been precontracted with a receptor agonist.

The effect of nisoldipine, used alone and in combination with nitroglycerin, on spasm of the internal mammary artery (IMA) showed that the combination of the two drugs produced a large positive synergistic effect in the prevention of contraction (Liu et al., 1994). These studies provide a scientific basis for combination of a calcium channel antagonist and nitric oxide (NO) donor for the most efficacious prevention of vasospasm and for relaxation of smooth muscle. Examples of systemic administration of nitroglycerin and nifedipine during cardiac surgery to prevent and treat myocardial ischemia or coronary artery vasospasm have been reported (Cohen et al., 1983; Seitelberger et al., 1991).

Calcium channel antagonists also exhibit synergistic effect with endothelin receptor subtype A (ET_A) antagonists. Yanagisawa and coworkers observed that dihydropyridine antagonists, calcium channel antagonists, blocked effects of ET-1_1 an endogenous agonist at the ET_A receptor in coronary arterial smooth muscle and hence speculated that ET-1 is an endogenous agonist of voltage-sensitive calcium channels. It has been found that the sustained phase of intracellular calcium elevation in smooth muscle cells induced by ET_A receptor activation requires extracellular calcium and is at least partially blocked by nicardipine. Thus, the inclusion of a calcium channel antagonist would be expected to synergistically enhance the actions of an ET_A antagonist when combined in a surgical solution.

Calcium channel antagonists and ATP-sensitive potassium channel openers likewise exhibit synergistic action. Potassium channels that are ATP-sensitive (K_{ATP}) couple the membrane potential of a cell to the cell's metabolic state via sensitivity to adenosine nucleotides. K_{ATP} channels are inhibited by intracellular ATP but are stimulated by intracellular nucleotide diphosphates. The activity of these channels is controlled by the electrochemical driving force to potassium and intracellular signals (e.g., ATP or a G-protein), but are not gated by the membrane potential per se. K_{ATP} channels hyperpolarize the membrane and thus allow them to control the resting potential of the cell. ATP-sensitive potassium currents have been discovered in skeletal muscle, brain, and vascular and nonvascular smooth muscle and binding studies with radiolabeled ligands have confirmed the existence of these channels which are the receptor targets for the potassium-channel opener drugs such as pinacidil. Opening of these channels causes potassium efflux and hyperpolarizes the cell membrane. This hyperpolarization (1) induces a reduction in intracellular free calcium through inhibition of voltage-dependent Ca^{2+} channels by reducing the opening probability of both L-type and T-type calcium channels, (2) restrains agonist induced (receptor operated channels) Ca^{2+} release from intracellular sources through inhibition of inositol triphosphate (IP3) formation, and (3) lowers the efficiency of calcium as an activator of contractile proteins. These combined actions of these two classes of drugs will clamp the target cells into a relaxed state or one which is more resistant to activation.

Finally, calcium channel antagonists and tachykinin and bradykinin antagonists exhibit synergistic effects in mediating neuroinflammation. The role of neurokinin receptors in mediating neuroinflammation has been established. The neurokinin$_1$ (NK1) and neurokinin$_2$ (NK2) receptor (members of the G-protein coupled superfamily) signal transduction pathway includes increases in intracellular calcium, thus leading to activation of calcium channels on the plasma membrane. Similarly, activation of bradykinin$_2$ (BK2) receptors is coupled to increases in intracellular calcium. Thus, calcium channel antagonists interfere with a common mechanism involving elevation of intracellular calcium, part of which enters through L-type channels. This is the basis for synergistic interaction between calcium channel antagonists and antagonists to these receptors.

Suitable calcium channel antagonists for the practice of the present invention include nisoldipine, nifedipine, nimodipine, lacidipine and isradipine. Suitable concentrations for these agents are set forth in Table 18.

Table 18
Therapeutic and Preferred Concentrations of Pain/Inflammation Inhibitory Agents

Agent	Therapeutic Concentrations (Nanomolar)	Preferred Concentrations (Nanomolar)
Calcium Channel Antagonists:		
nisoldipine	1-10,000	100-1,000
nifedipine	1-10,000	100-5,000
nimodipine	1-10,000	100-5,000
lacidipine	1-10,000	100-5,000
isradipine	1-10,000	100-5,000

P. Anti-Spasm Agents

1. Multifunction Agents

Several of the anti-pain/anti-inflammatory agents described above also serve to inhibit vasoconstriction or smooth muscle spasm. As such, these agents also perform the function of an anti-spasm agent, and thus are beneficially used in vascular and urinary applications. Anti-inflammatory/anti-pain agents that also serve as anti-spasm agents include: serotonin receptor antagonists, particularly, serotonin$_2$ antagonists; tachykinin receptor antagonists, ATP-sensitive potassium channel openers and calcium channel antagonists.

2. Nitric Oxide Donors

Nitric oxide donors may be included in the solutions of the present invention particularly for their anti-spasm activity. Nitric oxide (NO) plays a critical role as a molecular mediator of many physiological processes, including vasodilation and regulation of normal vascular tone. Within endothelial cells, an enzyme known as NO synthase (NOS) catalyzes the conversion of L-arginine to NO which acts as a diffusible second messenger and mediates responses in adjacent smooth muscle cells. NO is continuously formed and released by the vascular endothelium under basal conditions which inhibits contractions and controls basal coronary tone and is produced in the endothelium in response to various antagonists (such as acetylcholine)

and other endothelium dependent vasodilators. Thus, regulation of NO synthase activity and the resultant levels of NO are key molecular targets controlling vascular tone. Muramatsu, K., et. al., Coron. Artery Dis., Vol. 5, pp. 815-820 (1994).

Synergistic interactions between NO donors and openers of ATP-sensitive potassium channels (KCOs) are expected to achieve vasorelaxation or smooth muscle relaxation. A rationale for dual use is based upon the fact that these drugs have different molecular mechanisms of action in promoting relaxation of smooth muscle and prevention of vasospasm. There is evidence from cultured coronary arterial smooth muscle cells that the vasoconstrictors: vasopressin, angotensin II and endothelin, all inhibit K_{ATP} currents through inhibition of protein kinase A. In addition, it has been reported that K_{ATP} current in bladder smooth muscle is inhibited by muscarinic agonists. The actions of NO in mediating smooth relaxation occur via independent molecular pathways (described above) involving protein kinase G. This suggests that the combination of the two drugs will be more efficacious in relaxing smooth muscle than employing a single drug alone.

Suitable nitric oxide donors for the practice of the present invention include nitroglycerine, sodium nitroprusside, the drug FK409, 3-morpholinosydnonimine , or linsidomine chlorohydrate, ("SIN-1"); and S-nitroso-N-acetylpenicillamine ("SNAP"). Concentrations for these agents are set forth in Table 19.

Table 19

Therapeutic and Preferred Concentrations of Pain/Inflammation Inhibitory Agents

Agent	Therapeutic Concentrations (Nanomolar)	Preferred Concentrations (Nanomolar)
Nitric Oxide Donors:		
Nitroglycerin	10-10,000	100-1,000
sodium nitroprusside	10-10,000	100-1,000
SIN-1	10-10,000	100-1,000
SNAP	10-10,000	100-1,000
FK409	1-1,000	10-100

3. Endothelin Receptor Antagonists

Endothelin is a 21 amino acid peptide that is one of the most potent vasoconstrictors known. Three different human endothelin peptides, designated ET1, ET2 and ET3 have been described which mediate their physiological effects through at least two receptor subtypes referred to as ET_A and ET_B receptors. The heart and the vascular smooth muscles contain predominantly ET_A receptors and this subtype is responsible for contraction in these tissues. Furthermore, ET_A receptors have often been found to mediate contractile responses in isolated smooth muscle preparations. Antagonists of ET_A receptors have been found to be potent antagonists of human coronary artery contractions. Thus, antagonists to the ET_A receptor should be therapeutically beneficial in the perioperative inhibition of coronary vasospasm and may additionally be useful in inhibition of smooth muscle contraction in urological applications. Miller, R.C., et. al., Trends in Pharmacol. Sci., Vol. 14, pp. 54-60 (1993).

Suitable endothelin receptor antagonists include: cyclo(D-Asp-Pro-D-Val-Leu-D-Trp) ("BQ 123"); (N,N-hexamethylene)-carbamoyl-Leu-D-Trp-(CHO)-D-Trp-OH ("BQ 610"); (R)2-([R-2-[(s)-2-([1-hexahydro-1H-azepinyl]-carbonyl]amino-4-methyl-pentanoyl) amino-3-(3[1-methyl-1H-indodyl])propionylamino-3(2-pyridyl) propionic acid ("FR 139317"); cyclo(D-Asp-Pro-D-Ile-Leu-D-Trp) ("JKC 301"); cyclo(D-Ser-Pro-D-Val-Leu-D-Trp) ("JK 302"); and 5-(dimethylamino)-N-(3,4-dimethyl-5-isoxazolyl)-1-naphthalenesulphonamide ("BMS 182874"). Concentrations for a representative two of these agents is set forth in Table 20.

Table 20

Therapeutic and Preferred Concentrations of Pain/Inflammation Inhibitory Agents

Agent	Therapeutic Concentrations (Nanomolar)	Preferred Concentrations (Nanomolar)
Endothelin Receptor Antagonists:		
BQ 123	0.01-1,000	10-1,000
FR 139317	1-100,000	100-10,000

VI. Method of Application

The solution of the present invention has applications for a variety of operative/interventional procedures, including surgical and diagnostic and therapeutic

techniques. Applications include use as a perioperatively applied irrigation solution during arthroscopic surgery of anatomic joints, urological procedures and intravascular diagnostic and therapeutic procedures. As used herein throughout, the term "perioperative" is intended to mean application of the solution during the course of an operative or interventional medical procedure, and for many procedures will preferably also entail application of the solution prior to the initiation of the procedure. Such procedures conventionally utilize physiologic irrigation fluids, such as normal saline or lactated Ringer's, applied to the surgical site by techniques well know to those of ordinary skill in the art. The method of the present invention involves substituting the anti-pain/anti-inflammatory/anti-spasm irrigation solution of the present invention for conventionally applied irrigation fluids. The irrigation solution is applied to the wound or surgical site prior to the initiation of the procedure, preferably before tissue trauma, and continuously throughout the duration of the procedure, to preemptively block pain and inflammation and/or spasm. As used herein throughout, the term "irrigation" is intended to mean the flushing of a wound or anatomic structure with a stream of liquid. As used herein throughout, the term "continuously" is intended to also include situations in which there is repeated and frequent irrigation of wounds at a frequency sufficient to maintain a predetermined therapeutic local concentration of the applied agents, and applications in which there may be intermittent cessation of irrigation fluid flow necessitated by operating technique.

Arthroscopic techniques for which the present solution may be employed include, by way of non-limiting example, partial meniscectomies and ligament reconstructions in the knee, shoulder acromioplasties, rotator cuff debridements, elbow synovectomies, and wrist and ankle arthroscopies. The irrigation solution is continuously supplied intraoperatively to the joint at a flow rate sufficient to distend the joint capsule, to remove operative debris, and to enable unobstructed intra-articular visualization.

A suitable irrigation solution for control of pain and edema during such arthroscopic techniques is provided in Example I herein below. For arthroscopy, it is preferred that the solution include a combination, and preferably all, or any of the following: a serotonin$_2$ receptor antagonist, a serotonin$_3$ receptor antagonist, a histamine$_1$ receptor antagonist, a serotonin receptor agonist acting on the 1A, 1B, 1D, 1F and/or 1E receptors, a bradykinin$_1$ receptor antagonist, a bradykinin$_2$ receptor antagonist, and a cyclooxygenase inhibitor, and preferably all of the above agents.

This solution utilizes extremely low doses of these pain and inflammation inhibitors, due to the local application of the agents directly to the operative site during the procedure. For example, less than 0.05 mg of amitriptyline (a suitable serotonin$_2$ and histamine$_1$ "dual" receptor antagonist) is needed per liter of irrigation fluid to provide substantial local tissue concentrations that would inhibit 5-HT$_2$ and H$_1$ receptors. This dosage is extremely low relative to the 10-25 mg of oral amitriptyline that is the usual starting dose for this drug.

In each of the surgical solutions of the present invention, the agents are included in low concentrations and are delivered locally in low doses relative to concentrations and doses required with conventional methods of drug administration to achieve the desired therapeutic effect. It is impossible to obtain an equivalent therapeutic effect by delivering similarly dosed agents via other (i.e., intravenous, intramuscular or oral) routes of drug administration since drugs given systemically are subject to first- and second-pass metabolism.

For example, using a rat model of arthroscopy, the inventors examined the ability of amitriptyline, a 5-HT$_2$ antagonist, to inhibit 5-HT-induced plasma extravasation in the rat knee in accordance with the present invention. This study, described more fully below in Example VIII, compared the therapeutic dosing of amitriptyline delivered locally (i.e., intra-articularly) at the knee and intravascularly. The results demonstrated that intra-articular administration of amitriptyline required total dosing levels approximately 200-fold less than were required via the intravenous route to obtain the same therapeutic effect. Given that only a small fraction of the drug delivered intra-articularly is absorbed by the local synovial tissue, the difference in plasma drug levels between the two routes of administration is much greater than the difference in total amitriptyline dosing levels.

Practice of the present invention should be distinguished from conventional intra-articular injections of opiates and/or local anesthetics at the end of arthroscopic or "open" joint (e.g., knee, shoulder, etc.) procedures. The solution of the present invention is used for continuous infusion throughout the surgical procedure to provide preemptive inhibition of pain and inflammation. In contrast, the high concentrations necessary to achieve therapeutic efficacy with a constant infusion of local anesthetics, such as lidocaine (0.5-2% solutions), would result in profound systemic toxicity.

Upon completion of the procedure of the present invention, it may be desirable to inject or otherwise apply a higher concentration of the same pain and inflammation inhibitors as used in the irrigation solution at the operative site, as an alternative or supplement to opiates.

The solution of the present invention also has application in intravascular diagnostic and therapeutic procedures to potentially decrease vessel wall spasm, platelet aggregation and nociceptor activation produced by vessel manipulation. A suitable solution for such techniques is disclosed in Example II herein below. The intravascular solution preferably includes any combination, and preferably all, of the following: a 5-HT_2 receptor antagonist (Saxena, P. R., et. al., *Cardiovascular Effects of Serotonin Inhibitory Agonists and Antagonists*, J Cardiovasc Pharmacol 15 (Suppl. 7), pp. S17-S34 (1990); Douglas, 1985); a 5-HT_3 receptor antagonist to block activation of these receptors on sympathetic neurons and C-fiber nociceptive neurons in the vessel walls, which has been shown to produce brady- and tachycardia (Saxena et. al. 1990); a bradykinin$_1$ receptor antagonist; and a cyclooxygenase inhibitor to prevent production of prostaglandins at tissue injury sites, which decreases pain and inflammation. In addition, the intravascular solution also preferably will contain a serotonin$_{1B}$ (also known as serotonin$_{1D\beta}$) antagonist because serotonin has been shown to produce significant vascular spasm via activation of the serotonin$_{1B}$ receptors in humans. Kaumann, A.J., et al., *Variable Participation of 5-HT1-Like Receptors and 5-HT2 Receptors in Serotonin-Induced Contraction of Human Isolated Coronary Arteries*, Circulation 90, pp. 1141-53 (1994). This excitatory action of serotonin1B receptors in vessel walls, resulting in vasoconstriction, is in contrast to the previously-discussed inhibitory action of serotonin$_{1B}$ receptors in neurons. For the purpose of the intravascular solution, the term "pain/inflammation inhibitory agents" is intended to also include vessel wall spasm and platelet aggregation inhibitory agents.

The solution of the present invention also has utility for reducing pain and inflammation associated with urological procedures, such as trans-urethral prostate resection and similar urological procedures utilizing a laser. Studies have demonstrated that serotonin, histamine and bradykinin produce inflammation in lower urinary tract tissues. Schwartz, M.M., et. al., *Vascular Leakage in the Kidney and Lower Urinary Tract: Effects of Histamine, Serotonin and Bradykinin*, Proc Soc Exp Biol Med 140, pp. 535-539 (1972). A suitable irrigation solution for urological procedures is disclosed in Example III herein below. The solution preferably includes a combination, and preferably all, of the following: a histamine$_1$ receptor antagonist to inhibit histamine-induced pain and inflammation; a 5-HT_3 receptor antagonist to block activation of these receptors on peripheral C-fiber nociceptive neurons; a bradykinin$_1$ antagonist; a bradykinin$_2$ antagonist; and a cyclooxygenase inhibitor to decrease pain/inflammation produced by prostaglandins at the tissue injury sites.

Preferably an anti-spasm agent is also included to prevent spasm in the urethral canal and bladder wall spasm.

The solution of the present invention may also be employed perioperatively for the inhibition of pain and inflammation in surgical wounds, as well as to reduce pain and inflammation associated with burns. Burns result in the release of a significant quantity of biogenic amines, which not only produce pain and inflammation, but also result in profound plasma extravasation (fluid loss), often a life-threatening component of severe burns. Holliman, C.J., et. al., *The Effect of Ketanserin, a Specific Serotonin Antagonist, on Burn Shock Hemodynamic Parameters in a Porcine Burn Model*, J Trauma 23, pp. 867-871 (1983). The solution disclosed in Example I for arthroscopy may also be suitably applied to a wound or burn for pain and inflammation control. The agents of the solution of Example I may alternately be carried at the same concentrations in a paste or salve base, for application to the burn or wound.

VII. Examples

The following are several formulations in accordance with the present invention suitable for certain operative procedures followed by a summary of two clinical studies utilizing the agents of the present invention.

A. Example 1

Irrigation Solution for Arthroscopy

The following composition is suitable for use in anatomic joint irrigation during arthroscopic procedures. Each drug is solubilized in a carrier fluid containing physiologic electrolytes, such as normal saline or lactated Ringer's solution, as are the remaining solutions described in subsequent examples.

Class of Agent	Drug	Concentration (Nanomolar): Therapeutic	Preferred	Most Preferred
$serotonin_2$ antagonist	amitriptyline	0.1-1,000	50-500	100
$serotonin_3$ antagonist	metoclopramide	10-10,000	200-2,000	1,000
$histamine_1$ antagonist	amitriptyline	0.1-1,000	50-500	200
$serotonin_{1A, 1B, 1D, 1F}$ inhibitory agonist	sumatriptan	1-1,000	10-200	50
$bradykinin_1$ antagonist	[des-Arg^{10}]	1-1,000	50-500	200

	derivative of HOE 140			
bradykinin$_2$ antagonist	HOE 140	1-1,000	50-500	200

B. Example II

Irrigation Solution for Intravascular Therapeutic Procedures

The following drugs and concentration ranges in solution in a physiologic carrier fluid are suitable for use in irrigating operative sites during intravascular procedures.

Class of Agent	Drug	Concentration (Nanomolar): Therapeutic	Preferred	Most Preferred
serotonin$_2$ antagonist	trazodone	0.1-1,000	50-500	200
serotonin$_3$ antagonist	metoclopramide	10-10,000	200-2,000	1,000
serotonin$_{1B}$ antagonist	yohimbine	0.1-1,000	50-500	200
bradykinin$_1$ antagonist	[des-Arg^{10}] derivative of HOE 140	1-1,000	50-500	200
cyclooxygenase inhibitor	ketorolac	100-10,000	800-5,000	3,000

C. Example III

Irrigation Solution for Urologic Procedures

The following drugs and concentration ranges in solution in a physiologic carrier fluid are suitable for use in irrigating operative sites during urological procedures.

Class of Agent	Drug	Concentration (Nanomolar): Therapeutic	Preferred	Most Preferred
Histamine$_1$ antagonist	terfenadine	0.1-1,000	50-500	200
serotonin$_3$ antagonist	metoclopramide	10-10,000	200-2,000	1,000
bradykinin$_1$ antagonist	[des-Arg^{10}] derivative of HOE 140	1-1,000	50-500	200
bradykinin$_2$ antagonist	HOE 140	1-1,000	50-500	200
cyclooxygenase inhibitor	ketorolac	100-10,000	800-5,000	3,000

D. Example IV

Irrigation Solution for Arthroscopy, Burns, General Surgical Wounds and Oral/Dental Applications

The following composition is preferred for use in anatomic irrigation during arthroscopic and oral/dental procedures and the management of burns and general surgical wounds. While the solution set forth in Example I is suitable for use with the present invention, the following solution is even more preferred because of expected higher efficacy.

Class of Agent	Drug	Concentration (Nanomolar): Therapeutic	Preferred	Most Preferred
serotonin$_2$antagonist	amitriptyline	0.1 - 1,000	50 - 500	200
serotonin$_3$antagonist	metoclopramide	10 - 10,000	200 - 2,000	1,000
histamine$_1$antagonist	amitriptyline	0.1 - 1,000	50 - 500	200
serotonin $_{1A, 1B, 1D, 1F}$ agonist	sumatriptan	1 - 1,000	10 - 200	100
cyclooxygenase inhibitor	ketorolac	100 - 10,000	800 - 5,000	3,000
neurokinin$_1$antagonist	GR 82334	1 - 1,000	10 - 500	200
neurokinin$_2$antagonist	(±) SR 48968	1 - 1,000	10 - 500	200
purine$_{2X}$antagonist	PPADS	100 - 100,000	10,000-100,000	50,000
ATP-sensitive K^+ channel agonist	(-) pinacidil	1 - 10,000	100 - 1,000	500
Ca^{2+} channel antagonist	nifedipine	1 - 10,000	100 - 5,000	1,000
kallikrein inhibitor	aprotinin	0.1 - 1,000	50 - 500	200

E. Example V

Irrigation Solution for Intravascular Therapeutic Procedures

The following drugs and concentration ranges in solution in a physiologic carrier fluid are preferred for use in irrigating operative sites during intravascular procedures. Again, this solution is preferred relative to the solution set forth in Example II above for higher efficacy.

Class of Agent	Drug	Concentration (Nanomolar): Therapeutic	Preferred	Most Preferred
serotonin$_2$antagonist	trazodone	0.1 - 1,000	50 - 500	200
cyclooxygenase inhibitor	ketorolac	100 - 10,000	800 - 5,000	3,000
endothelin antagonist	BQ 123	0.01 - 1,000	10 - 1,000	500
ATP-sensitive K^+ channel agonist	(-) pinacidil	1 - 10,000	100 - 1,000	500
Ca^{2+} channel antagonist	nisoldipine	1 - 10,000	100 - 1,000	500
nitric oxide donor	SIN-1	10 - 10,000	100 - 1,000	500

F. Example VI

Irrigation Solution for Urologic Procedures

The following drugs and concentration ranges in solution in a physiologic carrier fluid are preferred for use in irrigating operative sites during urologic procedures. The solution is believes to have even higher efficacy than the solution set forth in prior Example III.

Class of Agent	Drug	Concentration (Nanomolar): Therapeutic	Preferred	Most Preferred
serotonin$_2$antagonist	LY 53857	0.1 - 500	1 - 100	50
histamine$_1$antagonist	terfenadine	0.1 - 1,000	50 - 500	200
cyclooxygenase inhibitor	ketorolac	100 - 10,000	800 - 5,000	3,000
neurokinin$_2$antagonist	SR 48968	1 - 1,000	10 - 500	200

purine$_{2X}$antagonist	PPADS	100 - 100,000	10,000 - 100,000	50,000
ATP-sensitive K^+ channel agonist	(-) pinacidil	1 - 10,000	100 - 1,000	500
Ca^{2+} channel antagonist	nifedipine	1 - 10,000	100 - 5,000	1,000
kallikrein inhibitor	aprotinin	0.1 - 1,000	50 - 500	200
nitric oxide donor	SIN-1	10 - 10,000	100 - 1,000	500

G. Example VII

Balloon Dilatation of Normal Iliac Arteries in the New Zealand White Rabbit and the Influence of Histamine/Serotonin Receptor Blockade on the Response

The purpose of this study was twofold. First, a new *in vivo* model for the study of arterial tone was employed. The time course of arterial dimension changes before and after balloon angioplasty is described below. Second, the role of histamine and serotonin together in the control of arterial tone in this setting was then studied by the selective infusion of histamine and serotonin receptor blocking agents into arteries before and after the angioplasty injury.

1. Design Considerations

This study was intended to describe the time course of change in arterial lumen dimensions in one group of arteries and to evaluate the effect of histamine/serotonin receptor blockade on these changes in a second group of similar arteries. To facilitate the comparison of the two different groups, both groups were treated in an identical manner with the exception of the contents of an infusion performed during the experiment. In control animals (arteries), the infusion was normal saline (the vehicle for test solution). The histamine/serotonin receptor blockade treated arteries received saline containing the blocking agents at the same rate and at the same part of the protocol as control animals. Specifically, the test solution included: (a) the serotonin$_3$ antagonist metoclopramide at a concentration of 16.0 μM; (b) the serotonin$_2$ antagonist trazodone at a concentration of 1.6μM; and (c) the histamine antagonist promethazine at concentrations of 1.0μM, all in normal saline. This study was performed in a prospective, randomized and blinded manner. Assignment to the specific groups was random and investigators were blinded to

infusion solution contents (saline alone or saline containing the histamine/serotonin receptor antagonists) until the completion of the angiographic analysis.

2. Animal Protocol

This protocol was approved by the Seattle Veteran Affairs Medical Center Committee on Animal Use and the facility is fully accredited by the American Association for Accreditation of Laboratory Animal Care. The iliac arteries of 3-4 kg male New Zealand white rabbits fed a regular rabbit chow were studied. The animals were sedated using intravenous xylazine (5 mg/kg) and Ketamine (35 mg/kg) dosed to effect and a cutdown was performed in the ventral midline of the neck to isolate a carotid artery. The artery was ligated distally, an arteriotomy performed and a 5 French sheath was introduced into the descending aorta. Baseline blood pressure and heart rate were recorded and then an angiogram of the distal aorta and bilateral iliac arteries was recorded on 35 mm cine film (frame rate 15 per second) using hand injection of iopamidol 76% (Squibb Diagnostics, Princeton, NJ) into the descending aorta. For each angiogram, a calibration object was placed in the radiographic field of view to allow for correction for magnification when diameter measurements were made. A 2.5 French infusion catheter (Advanced Cardiovascular Systems, Santa Clara, CA) was placed through the carotid sheath and positioned 1-2 cm above the aortic bifurcation. Infusion of the test solution -- either saline alone or saline containing the histamine/serotonin receptor antagonists -- was started at a rate of 5 cc per minute and continued for 15 minutes. At 5 minutes into the infusion, a second angiogram was performed using the previously described technique then a 2.5 mm balloon angioplasty catheter (the Lightning, Cordis Corp., Miami, FL) was rapidly advanced under fluoroscopic guidance into the left and then the right iliac arteries. In each iliac the balloon catheter was carefully positioned between the proximal and distal deep femoral branches using bony landmarks and the balloon was inflated for 30 seconds to 12 ATM of pressure. The balloon catheter was inflated using a dilute solution of the radiographic contrast agent so that the inflated balloon diameter could be recorded on cine film. The angioplasty catheter was rapidly removed and another angiogram was recorded on cine film at a mean of 8 minutes after the infusion was begun. The infusion was continued until the 15 minute time point and another angiogram (the fourth) was performed. Then the infusion was stopped (a total of 75 cc of solution had been infused) and the infusion catheter was removed. At the 30 minute time point (15 minutes after the infusion was stopped), a final angiogram was recorded as before. Blood pressure and heart rate were recorded at the 15 and

30 minute time points immediately before the angiograms. After the final angiogram, the animal was euthanized with an overdose of the anesthetic agents administered intravenously and the iliac arteries were retrieved and immersion fixed in formation for histologic analysis.

3. Angiographic Analysis

The angiograms were recorded on 35 mm cine film at a frame rate of 15 per second. For analysis, the angiograms were projected from a Vanguard projector at a distance of 5.5 feet. Iliac artery diameters at prespecified locations relative to the balloon angioplasty site were recorded based on hand held caliper measurement after correction for magnification by measurement of the calibration object. Measurements were made at baseline (before test solution infusion was begun), 5 minutes into the infusion, immediately post balloon angioplasty (a mean of 8 minutes after the test solution was begun), at 15 minutes (just before the infusion was stopped) and at 30 minutes (15 minutes after the infusion was stopped). Diameter measurements were made at three sites in each iliac artery: proximal to the site of balloon dilatation, at the site of balloon dilatation and just distal to the site of balloon dilatation.

The diameter measurements were then converted to area measurements by the formula:

$$\text{Area} = (\text{Pi})(\text{Diameter}^2)/4.$$

For calculation of vasoconstriction, baseline values were used to represent the maximum area of the artery and percent vasoconstriction was calculated as:

$$\%\ \text{Vasoconstriction} = \{\text{Baseline area} - \text{Later time point area}\}/\text{Baseline area}\} \times 100.$$

4. Statistical Methods

All values are expressed as mean ± 1 standard error of the mean. The time course of vasomotor response in control arteries was assessed using one way analysis of variance with correction for repeated measures. Post hoc comparison of data between specific time points was performed using the Scheffe test. Once the time points at which significant vasoconstriction occurred had been determined in control arteries, the control and histamine/serotonin receptor antagonist treated arteries were compared at those time points where significant vasoconstriction occurred in control arteries using multiple analysis of variance with treatment group identified as an independent variable. To compensate for the absence of a single a priori stated

hypothesis, a p value <0.01 was considered significant. Statistics were performed using Statistica for Windows, version 4.5, (Statsoft, Tulsa, OK).

5. Results

The time course of arterial dimension changes before and after balloon angioplasty in normal arteries receiving saline infusion was evaluated in 16 arteries from 8 animals (Table 21). Three segments of each artery were studied: the proximal segment immediately upstream from the balloon dilated segment, the balloon dilated segment and the distal segment immediately downstream from the balloon dilated segment. The proximal and distal segments demonstrated similar patterns of change in arterial dimensions: in each, there was significant change in arterial diameter when all time points were compared (proximal segment, p=0.0002 and distal segment, p<0.001, ANOVA). Post hoc testing indicated that the diameters at the immediate post angioplasty time point were significantly less than the diameters at baseline or at the 30 minute time point in each of these segments. On the other hand, the arterial diameters in each segment at the 5 minute, 15 minute and 30 minute time points were similar to the baseline diameters. The balloon dilated segment showed lesser changes in arterial dimension than the proximal and distal segments. The baseline diameter of this segment was 1.82±0.05 mm; the nominal inflated diameter of the balloon used for angioplasty was 2.5 mm and the actual measured inflated diameter of the balloon was 2.20±0.03 mm (p<0.0001 vs. baseline diameter of the balloon treated segment). Thus, the inflated balloon caused circumferential stretch of the balloon dilated segment, but there was only slight increase in lumen diameter from baseline to the 30 minute time point (1.82±0.05 mm to 1.94±0.07 mm, p=NS by post hoc testing).

Table 21

Angiographically determined lumen diameters at the specified times before and after balloon dilatation of normal iliac arteries.

Segment	Baseline	5 Minute	Immediate Post PTA	15 Minute	30 Minute
Proximal[1]	2.18±0.7	2.03±0.7	1.81±0.08*	2.00±.08	2.23±.08
Balloon[2]	1.82±.05	1.77±.03	1.79±.05	1.70±.04	1.94±.07
Distal[3]	1.76±.04	1.68±.04**	1.43±.04*	1.54±.03	1.69±.06

All measurements in mm. Means±SEM.PTA = percutaneous transluminal angioplasty. [1] p=0.0002 (ANOVA within group comparison),[2] p=0.03 (ANOVA within group comparison),

[3] $p<0.0001$ (ANOVA within group comparison). N=16 at all time points.
* $p<0.01$ versus baseline and 30 minute diameter measurements (Scheffe test for post hoc comparisons).
** $p<0.01$ versus immediate post PTA measurements (Scheffe test for post hoc comparisons). All other post hoc comparisons were not significant using the $p<0.01$ threshold.

Arterial lumen diameters were used to calculate lumen area then the area measurements were used to calculate percent vasoconstriction by comparison of the 5 minute, immediate post angioplasty, 15 and 30 minute data to the baseline measurements. The proximal and distal segment data expressed as percent vasoconstriction are shown in FIGURE 1; the changes in the amount of vasoconstriction over time are significant (in the proximal segment, $p=0.0008$; in the distal segment, $p=0.0001$, ANOVA). Post hoc testing identifies the vasoconstriction at the immediate post angioplasty time point as significantly different from that present at the 30 minute time point ($P<0.001$ in both segments). In the distal segment, the immediate post angioplasty vasoconstriction was also significantly less than that at 5 minutes ($p<0.01$); no other differences in intra-time point comparisons were significant by post hoc testing.

The luminal changes in control arteries can be summarized as follows: 1) Vasoconstriction with loss of approximately 30% of baseline luminal area occurs in the segments of artery proximal and distal to the balloon dilated segment immediately after balloon dilatation. There are trends to smaller amounts of vasoconstriction in the proximal and distal segments before dilatation and at the 15 minute time point (approximately 7 minutes after dilatation) also but, by the 30 minute time point (approximately 22 minutes after dilatation), a trend towards vasodilatation has replaced the previous vasoconstriction; 2) In the balloon dilated segment, only minor changes in lumen dimensions are present, and, despite the use of a balloon with a significantly larger inflated diameter than was present in this segment at baseline, there was no significant increase in lumen diameter of the dilated segment. These findings lead to a conclusion that any effects of the putative histamine/serotonin treatment would only be detectable in the proximal and distal segments at the time points where vasoconstriction was present.

The histamine/serotonin receptor blockade solution was infused into 16 arteries (8 animals); angiographic data was available at all time points in 12 arteries. Heart rate and systolic blood pressure measurements were available in a subset of animals (Table 22). There were no differences in heart rate or systolic blood pressure when the two animal groups were compared within specific time

points. Histamine/serotonin treated animals showed trends toward a decrease in the systolic blood pressure from baseline to 30 minutes (-14±5 mm Hg, p=0.04) and a lower heart rate (-26±10, p=0.05). Within the control animals, there was no change in heart rate or systolic blood pressure over the duration of the experiment.

Table 22

Systolic blood pressure and heart rate measurements in control and histamine/serotonin treated animals.

Group	Baseline (N)	5 Minute (N)	15 Minute (N)	30 Minute (N)
Systolic Blood Pressure				
Control	83±4 (8)	84±4 (8)	82±6 (8)	80±4 (8)
Histamine/Serotonin	93±5 (6)	87±9 (4)	82±9 (6)	80±8 (6)*
Heart Rate				
Control	221±18 (5)	234±18 (4)	217±23 (5)	227±22 (5)
Histamine/Serotonin	232±8 (5)	232±8 (5)	209±14 (5)	206±12 (5)**

Systolic blood pressure in mm Hg and heart rate in beats per minute. Mean±SEM.
* p=0.04 for decrease in systolic blood pressure from baseline to 30 minutes and
**p=0.05 for decrease in heart rate from baseline to 30 minutes within the histamine/serotonin treated animals.

The proximal and distal segments of histamine/serotonin treated arteries were compared to control arteries using the percent vasoconstriction measurement. FIGURE 2A shows the effects of the histamine/serotonin infusion on proximal segment vasoconstriction relative to the vasoconstriction present in the control arteries. When the findings in the two treatment groups were compared at the baseline immediate post angioplasty and 15 minute time point, histamine/serotonin infusion resulted in significantly less vasoconstriction compared to the control saline infusion (p=0.003. 2-way ANOVA). Comparison of the two treatment groups in the distal segment is illustrated in FIGURE 2B. Despite observed differences in mean diameter measurements in the distal segment, solution treated vessels exhibited less vasoconstriction than saline treated control vessels at baseline, immediate post-angioplasty and 15 minute time points, this pattern did not achieve statistical significance (p=0.32, 2-way ANOVA). Lack of statistical significance may be attributed to smaller than expected vasoconstriction valves in the control vessels.

H. Example VIII

Amitriptyline Inhibition of 5-Hydroxytryptaniine-Induced Knee Joint Plasma Extravasation - Comparison of Intra-Articular Versus Intravenous Routes of Administration

The following study was undertaken in order to compare two routes of administration of the 5-HT_2 receptor antagonist, amitriptyline: 1) continuous intra-articular infusion; versus 2) intravenous injection, in a rat knee synovial model of inflammation. The ability of amitriptyline to inhibit 5-HT-induced joint plasma extravasation by comparing both the efficacy and total drug dose of amitriptyline delivered via each route was determined.

1. Animals

Approval from the Institutional Animal Care Committee at the University of California, San Francisco was obtained for these studies. Male Sprague-Dawley rats (Bantin and Kingman, Fremont, CA) weighing 300 - 450 g were used in these studies. Rats were housed under controlled lighting conditions (lights on 6 A.M. to 6 P.M.), with food and water available *ad libitum*.

2. Plasma Extravasation

Rats were anesthetized with sodium pentobarbital (65 mg/kg) and then given a tail vein injection of Evans Blue dye (50 mg/kg in a volume of 2.5 ml/kg), which is used as a marker for plasma protein extravasation. The knee joint capsule was exposed by excising the overlying skin, and a 30-gauge needle was inserted into the joint and used for the infusion of fluid. The infusion rate (250 µl/min) was controlled by a Sage Instruments Syringe pump (Model 341B, Orion Research Inc., Boston, MA). A 25-gauge needle was also inserted into the joint space and perfusate fluid was extracted at 250 µl/min, controlled by a Sage Instruments Syringe pump (Model 351).

The rats were randomly assigned to three groups: 1) those receiving only intra-articular (IA) 5-HT (1 µM), 2) those receiving amitriptyline intravenously (IV) (doses ranging from 0.01 to 1.0 mg/kg) followed by IA 5-HT (1 mM), and 3) those receiving amitriptyline intra-articularly (IA) (concentrations ranging from 1 to 100 nM) followed by IA 5-HT (1 µM) plus IA amitriptyline. In all groups, baseline plasma extravasation levels were obtained at the beginning of each experiment by perfusing 0.9% saline intra-articularly and collecting three perfusate samples over a 15 min. period (one every 5 min). The first group was then administered 5-HT IA for a total of 25 min. Perfusate samples were collected every 5 min for a total of 25 min.

Samples were then analyzed for Evans Blue dye concentration by spectrophotometric measurement of absorbance at 620 nm, which is linearly related to its concentration (Carr and Wilhelm, 1964). The IV amitriptyline group was administered the drug during the tail vein injection of the Evans Blue dye. The knee joints were then perfused for 15 min with saline (baseline), followed by 25 min perfusion with 5-HT (1 μM). Perfusate samples were collected every 5 min for a total of 25 min. Samples were then analyzed using spectrophotometry. In the IA amitriptyline group, amitriptyline was perfused intra-articularly for 10 min after the 15 min saline perfusion, then amitriptyline was perfused in combination with 5-HT for an additional 25 min. Perfusate samples were collected every 5 min and analyzed as above.

Some rat knees were excluded from the study due to physical damage of knee joint or inflow and outflow mismatch (detectable by presence of blood in perfusate and high baseline plasma extravasation levels or knee joint swelling due to improper needle placement).

a. 5-HT-Induced Plasma Extravasation

Baseline plasma extravasation was measured in all knee joints tested (total n=22). Baseline plasma extravasation levels were low, averaging 0.022 ± 0.003 absorbance units at 620 nm (average $\pm$ standard error of the mean). This baseline extravasation level is shown in Figures 1 and 2 as a dashed line.

5-HT (1 μM) perfused into the rat knee joint produces a time-dependent increase in plasma extravasation above baseline levels. During the 25 min perfusion of 5-HT intra-articularly, maximum levels of plasma extravasation were achieved by 15 min and continued until the perfusion was terminated at 25 min (data not shown). Therefore, 5-HT-induced plasma extravasation levels reported are the average of the 15, 20 and 25 min time points during each experiment. 5-HT-induced plasma extravasation averaged 0.192 ± 0.011, approximately an 8-fold stimulation above baseline. This data is graphed in FIGURES 3 and 4, corresponding to the "0" dose of IV amitriptyline and the "0" concentration of IA amitriptyline, respectively.

b. Effect of Intravenous Amitriptyline on 5-HT-Induced Plasma Extravasation

Amitriptyline administered via tail vein injection produced a dose-dependent decrease in 5-HT-induced plasma extravasation as shown in FIGURE 3. The IC_{50} for IV amitriptyline inhibition of 5-HT-induced plasma extravasation is approximately 0.025 mg/kg. 5-HT-induced plasma extravasation is completely inhibited by an IV amitriptyline dose of 1 mg/kg, the plasma extravasation averaging 0.034 ± 0.010.

c. Effect of Intra-articular amitriptyline on 5-HT-Induced Plasma Extravasation

Amitriptyline administered alone in increasing concentrations intra-articularly did not affect plasma extravasation levels relative to baseline, with the plasma extravasation averaging 0.018 ± 0.002 (data not shown). Amitriptyline co-perfused in increasing concentrations with 5-HT produced a concentration-dependent decrease in 5-HT-induced plasma extravasation as shown in FIGURE 4. 5-HT-induced plasma extravasation in the presence of 3 nM IA amitriptyline was not significantly different from that produced by 5-HT alone, however, 30 nM amitriptyline co-perfused with 5-HT produced a greater than 50% inhibition, while 100 nM amitriptyline produced complete inhibition of 5-HT-induced plasma extravasation. The IC_{50} for IA amitriptyline inhibition of 5-HT-induced plasma extravasation is approximately 20 nM.

The major finding of the present study is that 5-HT (1 μM) perfused intra-articularly in the rat knee joint produces a stimulation of plasma extravasation that is approximately 8-fold above baseline levels and that either intravenous or intra-articular administration of the 5-HT_2 receptor antagonist, amitriptyline, can inhibit 5-HT-induced plasma extravation. The total dosage of administered amitriptyline, however, differs dramatically between the two methods of drug delivery. The IC_{50} for IV amitriptyline inhibition of 5-HT-induced plasma extravasation is 0.025 mg/kg, or 7.5×10^{-3} mg in a 300 g adult rat. The IC_{50} for IA amitriptyline inhibition of 5-HT-induced plasma extravasation is approximately 20 nM. Since 1 ml of this solution was delivered every five minutes for a total of 35 min during the experiment, the total dosage perfused into the knee was 7 ml, for a total dosage of 4.4×10^{-5} mg perfused into the knee. This IA amitriptyline dose is approximately 200-fold less than the IV amitriptyline dose. Furthermore, it is likely that only a small fraction of the IA perfused drug is systemically absorbed, resulting in an even greater difference in the total delivered dose of drug.

Since 5-HT may play an important role in surgical pain and inflammation, as discussed earlier, 5-HT antagonists such as amitriptyline may be beneficial if used during the perioperative period. A recent study attempted to determine the effects of oral amitriptyline on post-operative orthopedic pain (Kerrick et al., 1993). An oral dose as low as 50 mg produced undesirable CNS side-effects, such as a "decreased feeling of well-being". Their study, in addition, also showed that oral amitriptyline produced higher pain scale scores than placebo (P0.05) in the post-operative patients. Whether this was due to the overall unpleasantness produced by oral amitriptyline is not known. In contrast, an intra-articular route of administration allows extremely

low-concentration of drug to be delivered locally to the site of inflammation, possibly resulting in maximal benefit with minimal side-effects.

While the preferred embodiment of the invention has been illustrated and described, it will be appreciated that various changes to the disclosed solutions and methods can be made therein without departing from the spirit and scope of the invention. For example, alternate pain inhibitors and anti-inflammation and anti-spasm agents may be discovered that may augment or replace the disclosed agents in accordance with the disclosure contained herein. It is therefor intended that the scope of letters patent granted hereon be limited only by the definitions of the appended claims.

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A method for perioperatively inhibiting pain and inflammation, or spasm, or pain and inflammation and spasm, at a wound, comprising irrigating the wound during a medical procedure with a dilute solution of a plurality of inhibitory agents selected from pain/inflammation inhibitory agents and spasm inhibitory agents in a physiologic liquid carrier, the plurality of agents being selected from a plurality of classes of agents that act through differing molecular mechanisms of action at a plurality of receptors and enzymes mediating pain and inflammation or spasm, the agents collectively being effective for the inhibition of pain and inflammation, or spasm, or pain and inflammation and spasm at the wound.

2. The method of Claim 1, comprising continuously irrigating the wound with the solution during the medical procedure.

3. The method of Claim 1, wherein each agent is included at a concentration of no greater than 100,000 nanomolar.

4. The method of Claim 3, wherein each agent is included at a concentration of no greater than 10,000 nanomolar.

5. The method of Claim 1, wherein the classes of agents comprise pain/inflammation inhibitory agent classes selected from the group consisting of: serotonin receptor antagonists; serotonin receptor agonists; histamine receptor antagonists; bradykinin receptor antagonists; kallikrein inhibitors; neurokinin receptor antagonists including neurokinin$_1$ receptor subtype antagonists and neurokinin$_2$ receptor subtype antagonists; calcitonin gene-related peptide receptor antagonists; interleukin receptor antagonists; phospholipase inhibitors including PLA_2 isoform and PLC_γ isoform inhibitors; cyclooxygenase inhibitors; lipooxygenase inhibitors; prostanoid receptor antagonists including eicosanoid EP-1 and EP-4 receptor subtype antagonists and thromboxane receptor subtype antagonists; leukotriene receptor antagonists including leukotriene B_4 and D_4 receptor subtype antagonists; opioid receptor agonists including mu-opiate receptor subtype agonists, delta-opiate receptor subtype agonists, and kappa-opiate receptor subtype agonists; purinoceptor agonists and antagonists including P_{2Y} receptor agonists and P_{2X} receptor antagonists; ATP-sensitive potassium channel openers; and calcium channel antagonists.

6. The method of Claim 5, wherein the selected pain/inflammation inhibitory agents are included at concentrations of: 0.1 to 10,000 nanomolar for serotonin receptor antagonists; 0.1 to 2,000 nanomolar for serotonin receptor agonists; 0.1 to 1,000 nanomolar for histamine receptor antagonists; 1 to 10,000 nanomolar for bradykinin receptor antagonists; 0.1 to 1,000 nanomolar for kallikrein inhibitors; 0.1 to 10,000 nanomolar for neurokinin$_1$ receptor subtype antagonists; 1.0 to 10,000 nanomolar for neurokinin$_2$ receptor subtype antagonists; 1 to 1,000 nanomolar for calcitonin gene-related peptide antagonists; 1 to 1,000 nanomolar for interleukin antagonists; 100 to 100,000 nanomolar for PLA_2 isoform inhibitors; 100 to 200,000 nanomolar for cyclooxygenase inhibitors; 100 to 10,000 nanomolar for lipooxygenase inhibitors; 100 to 10,000 nanomolar for eicosanoid EP-1 receptor subtype antagonists; 100 to 10,000 nanomolar for leukotriene B_4 receptor subtype antagonists; 0.1 to 100 nanomolar for mu-opiate receptor subtype agonists; 0.1 to 500 nanomolar for delta-opiate receptor subtype agonists; 0.1 to 500 nanomolar for kappa-opiate receptor subtype agonists; 100 to 100,000 nanomolar for purinoceptor antagonists; 0.1 to 10,000 nanomolar for ATP-sensitive potassium channel openers; and 1.0 to 10,000 nanomolar for calcium channel antagonists.

7. The method of Claim 1, wherein the solution comprises an anti-spasm agent for the inhibition of vascular or smooth muscle spasm.

8. The method of Claim 7, wherein the anti-spasm agent or agents is selected from the group consisting of serotonin$_2$ receptor subtype antagonists, tachykinin receptor antagonists, nitric oxide donors, ATP-sensitive potassium channel openers, calcium channel antagonists, and endothelin receptor antagonists.

9. The method of Claim 8, wherein the selected anti-spasm agent or agents are included at concentrations of: 0.1 to 10,000 nanomolar for serotonin$_2$ receptor antagonists; 0.1 to 10,000 nanomolar for tachykinin receptor antagonists; 1.0 to 10,000 nanomolar for nitric oxide donors; 0.1 to 10,000 nanomolar for ATP-sensitive potassium channel openers; 1.0 to 10,000 nanomolar for calcium channel antagonists; and 0.01 to 100,000 nanomolar for endothelin receptor antagonists.

10. The method of Claim 1, wherein the irrigating comprises irrigating a vascular structure during an intravascular medical procedure.

11. The method of Claim 10, wherein the irrigation solution utilized includes at least one selected anti-spasm agent and at least one selected pain/inflammation inhibitory agent, the selected agents comprising: a serotonin$_2$ receptor subtype antagonist included at a concentration of 50 to 500 nanomolar; a cyclooxygenase inhibitor included at a concentration of 800 to 5,000 nanomolar; an endothelin receptor antagonist included at a concentration of 10 to 1,000 nanomolar; an ATP-sensitive potassium channel opener included at a concentration of 100 to 1,000 nanomolar; a calcium channel antagonist included at a concentration of 100 to 1,000 nanomolar; and a nitric oxide donor included at a concentration of 100 to 1,000 nanomolar.

12. The method of Claim 1, wherein the irrigating step comprises irrigating a surgical wound, a burn wound, or an anatomic joint during arthroscopic surgery.

13. The method of Claim 12, wherein the solution includes selected pain/inflammation inhibitory agents which comprise: a serotonin$_2$ receptor antagonist included at a concentration of 50 to 500 nanomolar; a serotonin$_3$ receptor antagonist included at a concentration of 200 to 2,000 nanomolar; a histamine$_1$ receptor antagonist included at a concentration of 50 to 500 nanomolar; a serotonin receptor agonist included at a concentration of 10 to 200 nanomolar; a cyclooxygenase inhibitor included at a concentration of 800 to 5,000 nanomolar; a neurokinin$_1$ receptor subtype antagonist included at a concentration of 10 to 500 nanomolar; a neurokinin$_2$ receptor subtype antagonist included at a concentration of 10 to 500 nanomolar; a purinoceptor antagonist included at a concentration of 10,000 to 100,000 nanomolar; an ATP-sensitive potassium channel opener included at a concentration of 100 to 1,000 nanomolar; a calcium channel antagonist included at a concentration of 100 to 5,000 nanomolar; and a kallikrein inhibitor included at a concentration of 50 to 500 nanomolar.

14. The method of Claim 1, wherein the irrigating step comprises irrigating at least a portion of the urinary tract during a urological procedure.

15. The method of Claim 14, wherein the irrigation solution utilized includes at least one selected anti-spasm agent and at least one selected pain/inflammation inhibitory agent, the selected agents comprising: a serotonin$_2$ receptor subtype antagonist included at a concentration of 1 to 100 nanomolar; a histamine$_1$ receptor subtype antagonist included at a concentration of 50 to 500

nanomolar; a cyclooxygenase inhibitor included at a concentration of 800 to 5,000 nanomolar; a neurokinin$_2$ receptor subtype antagonist included at a concentration of 10 to 500 nanomolar; a purinoceptor antagonist included at a concentration of 10,000 to 100,000 nanomolar; an ATP-sensitive potassium channel opener included at a concentration of 100 to 1,000 nanomolar; a calcium channel antagonist included at a concentration of 100 to 5,000 nanomolar; a kallikrein inhibitor included at a concentration of 50 to 500 nanomolar; and a nitric oxide donor included at a concentration of 100 to 1,000 nanomolar.

16. The method of Claim 1, wherein the solution includes a serotonin receptor antagonist.

17. The method of Claim 1, wherein the solution includes an ATP-sensitive potassium channel agonist.

18. The method of Claim 1, wherein the solution includes a calcium channel antagonist at a concentration of no more than 100,000.

19. A solution for perioperatively inhibiting pain and inflammation, or spasm, or pain and inflammation and spasm, for use in irrigating a wound during a medical procedure, comprising a dilute solution of a plurality of inhibitory agents selected from pain/inflammation inhibitory agents and spasm inhibitory agents in a physiologic liquid carrier, the plurality of agents being selected from a plurality of classes of agents that act through differing molecular mechanisms of action at a plurality of receptors and enzymes mediating pain and inflammation or spasm, the agents collectively being effective for the inhibition of pain and inflammation, or spasm, or pain and inflammation and spasm, at the wound.

20. The solution of Claim 19, wherein the classes of agents comprise pain/inflammation inhibitory agent classes selected from the group consisting of: serotonin receptor antagonists; serotonin receptor agonists; histamine receptor antagonists; bradykinin receptor antagonists; kallikrein inhibitors; neurokinin receptor antagonists including neurokinin$_1$ receptor subtype antagonists and neurokinin$_2$ receptor subtype antagonists; calcitonin gene-related peptide antagonists; interleukin antagonists; phospholipase inhibitors including PLA_2 isoform and PLC_γ isoform inhibitors; cyclooxygenase inhibitors; lipooxygenase inhibitors; prostanoid receptor

antagonists including eicosanoid EP-1 and EP-4 receptor subtype antagonists and thromboxane receptor subtype antagonists; leukotriene receptor antagonists including leukotriene B_4 and D_4 receptor subtype antagonists; opioid receptor agonists including mu-opiate receptor subtype agonists, delta-opiate receptor subtype agonists, and kappa-opiate receptor subtype agonists; purinoceptor agonists and antagonists including P_{2Y} receptor agonists and P_{2X} receptor antagonists; ATP-sensitive potassium channel openers; and calcium channel antagonists.

21. The solution of Claim 20, wherein the pain/inflammation inhibitory agents in the irrigation solution are included at concentrations of: 0.1 to 10,000 nanomolar for serotonin receptor antagonists; 0.1 to 2,000 nanomolar for serotonin receptor agonists; 0.1 to 1,000 nanomolar for histamine receptor antagonists; 1 to 10,000 nanomolar for bradykinin receptor antagonists; 0.1 to 1,000 nanomolar for kallikrein inhibitors; 0.1 to 10,000 nanomolar for neurokinin$_1$ receptor subtype antagonists; 1.0 to 10,000 nanomolar for neurokinin$_2$ receptor subtype antagonists; 1 to 1,000 nanomolar for calcitonin gene-related peptide receptor antagonists; 1 to 1,000 nanomolar for interleukin receptor antagonists; 100 to 100,000 nanomolar for phospholipase inhibitors; 100 to 200,000 nanomolar for cyclooxygenase inhibitors; 100 to 10,000 nanomolar for lipooxygenase inhibitors; 100 to 10,000 nanomolar for eicosanoid EP-1 receptor antagonists; 100 to 10,000 nanomolar for leukotriene B_4 receptor antagonists; 0.1 to 100 nanomolar for mu-opiate receptor subtype agonists; 0.1 to 500 nanomolar for delta-opiate receptor subtype agonists; 0.1 to 500 nanomolar for kappa-opiate receptor subtype agonists; 100 to 100,000 nanomolar for purinoceptor antagonists; 0.1 to 10,000 nanomolar for ATP-sensitive potassium channel openers; and 1.0 to 10,000 nanomolar for calcium channel antagonists.

22. The solution of Claim 19, wherein at least one of the selected classes of agents in the irrigation solution comprises a class of anti-spasm agents for inhibiting vascular spasm or smooth muscle spasm.

23. The solution of Claim 21, wherein the anti-spasm agents are selected from the group consisting of: serotonin$_2$ receptor subtype antagonists; tachykinin receptor antagonists; nitric oxide donors; ATP-sensitive potassium channel openers; calcium channel antagonists; and endothelin receptor antagonists.

24. The solution of Claim 23, wherein the anti-spasm agents are included at concentrations of: 0.1 to 10,000 nanomolar for serotonin$_2$ receptor subtype

antagonists; 0.1 to 10,000 nanomolar for tachykinin receptor antagonists; 1.0 to 10,000 nanomolar for nitric oxide donors; 0.1 to 10,000 nanomolar for ATP-sensitive potassium channel openers; 1.0 to 10,000 nanomolar for calcium channel antagonists; and 0.01 to 100,000 nanomolar for endothelin receptor antagonists.

25. The solution of Claim 19, wherein each agent is included at a concentration of no more than 100,000 nanomolar.

26. The solution of Claim 25, wherein each agent is included at a concentration of no more than 10,000 nanomolar.

FIG. 1

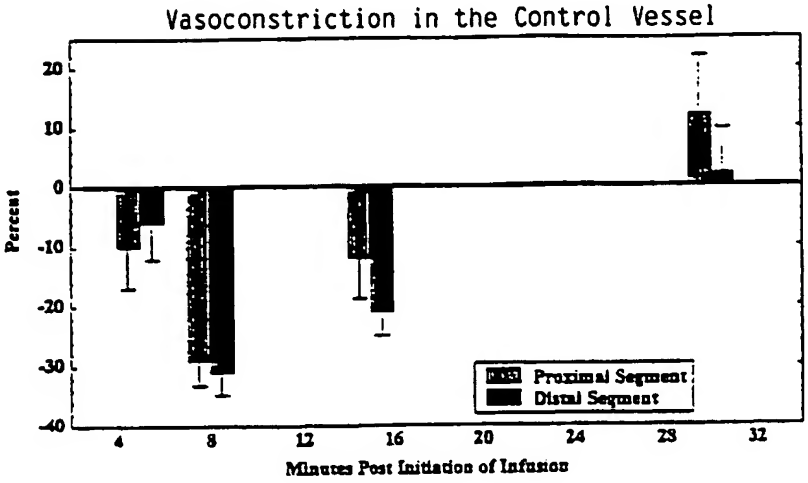


FIG. 2A

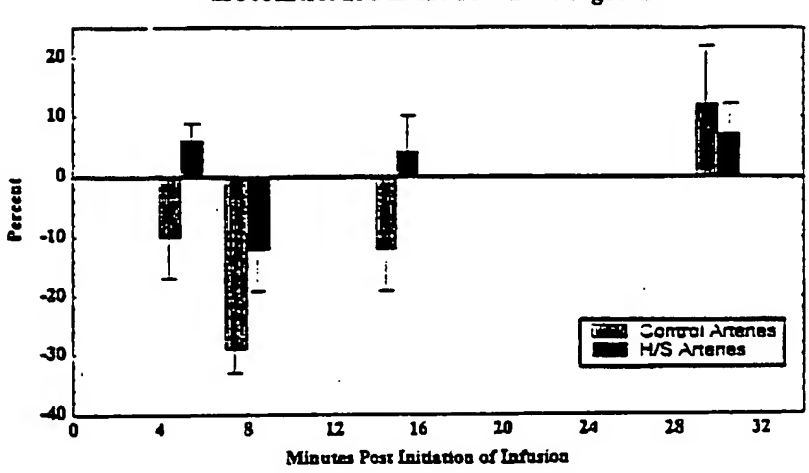
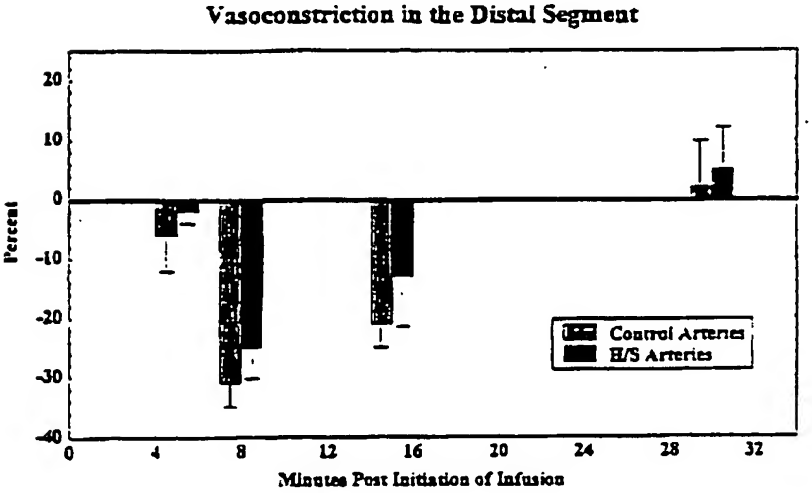


FIG.2B



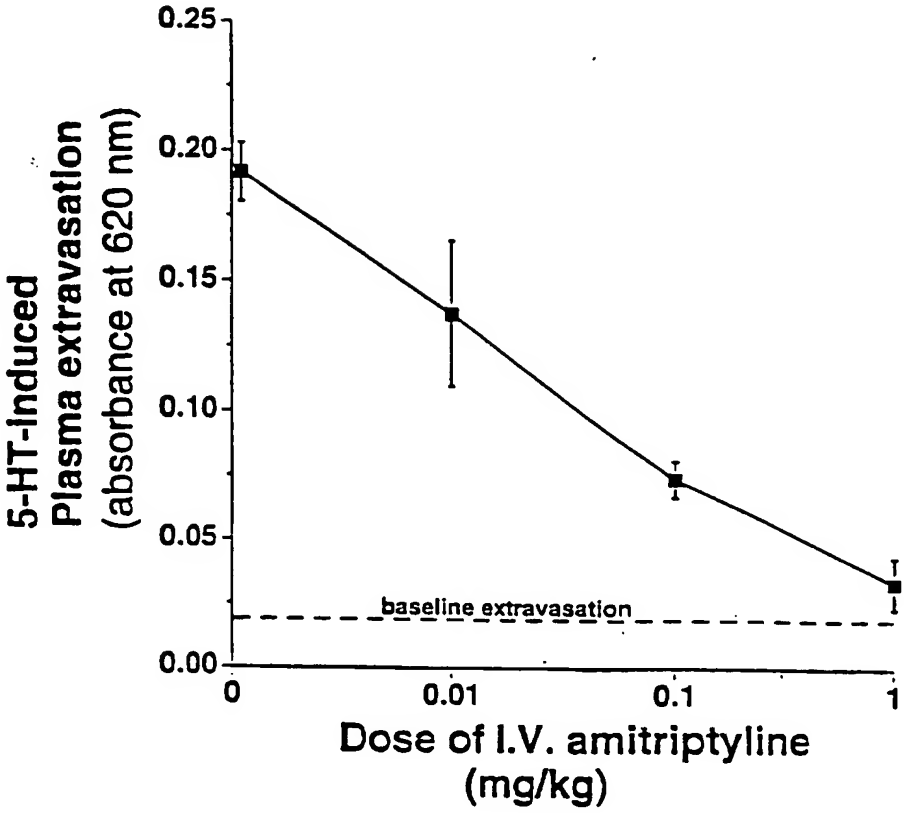

0.25
0.20
0.15
0.10
0.05
0.00
5-HT-Induced
Plasma extravasation
(absorbance at 620 nm)
baseline extravasation
0
0.01
0.1
1
Dose of I.V. amitriptyline
(mg/kg)

FIG. 3

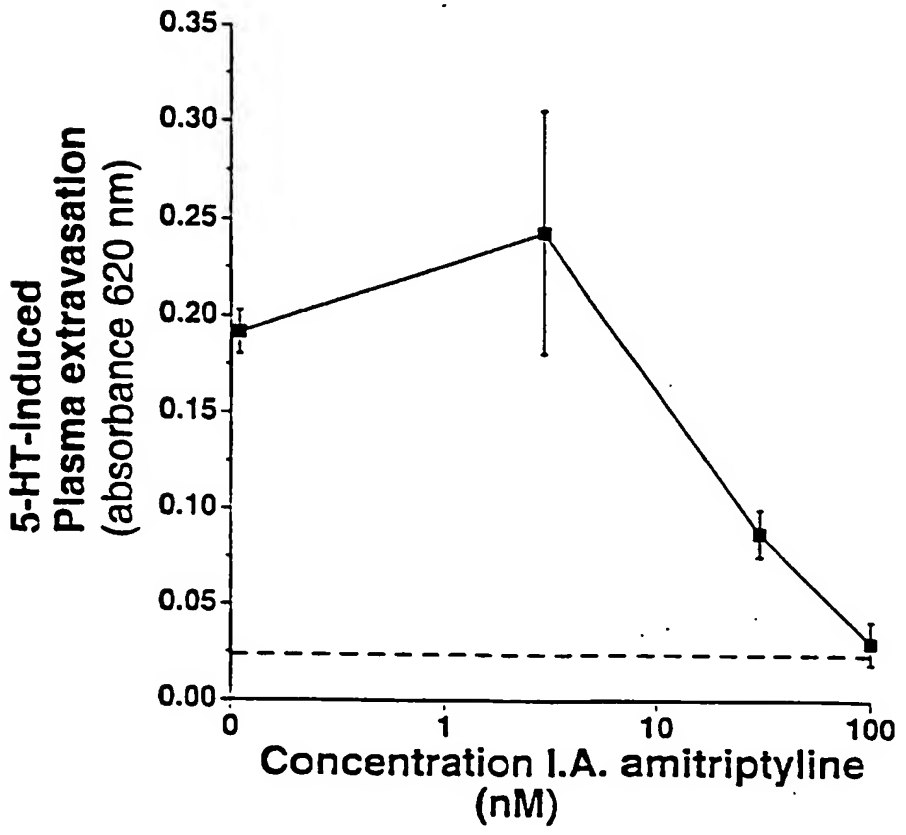

0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
5-HT-Induced
Plasma extravasation
(absorbance 620 nm)
0
1
10
100
Concentration I.A. amitriptyline
(nM)

FIG. 4